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PSYCHOPHARMACOLOGY ABSTRACTS

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ABSTRACTS

PRECLINICAL PSYCOPHARMACOLOGY

01 CHEMICAL SYNTHESIS, ISOLATION AND CHARACTERIZATION

066815 Klemm, Leroy H. University of Oregon, Eugene, Oregon Project Summary: Thienopyridine analogs of serotonin and tryptophan. Final Report, NIMH Grant MH-17304, 1970. 17 p.

It was proposed to prepare thieonpyridine analogs of tryptamine, tryptophan, melatonin, and serotonin for use (by others) on biological testing. Key steps in the proposed preparation involved direct chloromethylation and formylation of thieno/2,3-b/pyridine (I) at C-3. However, neither of these reactions could be effected. In an alternative approach, a study of direct halogenation of I was made. Results of the I reaction are summarized and it is noted that the desired 3-bromo derivative of I was readily obtained. The 3-iodo derivative of I was also prepared, but chlorination of I led to a variety of chemically interesting products, including the 3-chloro and 2,3-chloro derivatives, 2,3-dichloro 2,3-dihydro derivative of a sulfoxide of I, and a sulfone. Schemes are presented for conversion of these compounds to compounds expected to be useful in preparing the desired analogs. A practical 4 step synthesis of thieno/3,4-c/pyridine was achieved from the commercially available 3,4-dimethylpyridine. This thienopyridine was the last of 6 possible thienopyridines to be synthesized. At this point, success has not been attained for all of the synthetic goals sought, but it appears that preparation of 2-thieno/2,3-b/pyridine analogs of tryptamine and 2 of tryptophan should be forthcoming with limited additional work. It was not possible to proceed with syntheses of analogs of serotonin and melatonin. (Author abstract modified)

02 DRUG DEVELOPMENT (PRECLINICAL SCREENING)

064842 Matsumiya, Y.; Kling, J. W. Department of Neurology, Harvard Medical School, Boston, Massachusetts Conditioned suppression based on positively reinforcing intracranial stimulation. *Japanese Psychological Research (Tokyo).* 12(1):26-35, 1970.

Conditioned suppression based on positively reinforcing intracranial stimulation is investigated. Food reinforced barpressing behavior of rats was suppressed when a sound previously had been paired with posterior hypothalamic stimulation was acitivated by each barpress. This suppression was not observed in groups in which septal stimulation was used, or in which 200 'free' posterior hypothalamic stimulations were given before pairing. However, the suppression did appear if animals were anesthetized during the 'free' posterior hypothalamic stimulations. In later self-stimulation tests, intracranial stimuli at both sites were revealed as positively reinforcing. It is hypothesized that posterior hypothalamic stimulation initially has aversive components but that these diminish with additional stimulations. This shift in the characteristics of the stimulation does not seem attributable to tissue changes in the brain. 26 references. (Author abstract modified)

03 MECHANISM OF ACTION - PHYSIOLOGICAL, BIOCHEMICAL AND PHARMACOLOGICAL

064635 No author. Author address not given Can we brainwash the appetite? *Medical World News.* 11(39):20-21, 1970.

The ventrolateral hypothalamus is a center for appetite stimulation, while the ventromedial hypothalamus is concerned with gastronomic satiety. A lack of norepinephrine producing cells in the medial hypothalamus produces overeating in rats, and it is possible that noradrenergic cells adjacent to the hypothalamus send axons into the lateral hypothalamus to suppress hunger. These results prompt Dr. David Margules to speculate that the trend is approaching for clinical testing of biochemical therapy aimed at the hypothalamus of the chronically obese. Rockefeller University psychologist Dr. Sarah Leibowitz reports that dexedrine can either suppress or stimulate appetite depending on whether it is injected into the lateral or medial hypothalamus, demonstrating an alpha-adrenergic factor for hunger induction, and a beta-adrenergic system for satiation. Administration of norepinephrine produces a predominant alpha-adrenergic effect of hunger induction in rats, and is known to reduce thirst.

065332 Goldfoot, David A.; Goy, Robert W. Rotterdam Medical Faculty, Rotterdam, The Netherlands Abbreviation of behavioral estrus in guinea

***pigs by coital and vigino-cervical stimulation. Journal of Comparative and Physiological Psychology.* 72(3):426-434, 1970.**

The display of lordosis by an estrous female guinea pig in response to manual stimulation of the rump or in response to mounting by a male is terminated by the experience of coitus. Without the experience of coitus, lordosis can be elicited repeatedly for 6 to 8 hr. when the female is in either spontaneous or induced estrus. Mechanical stimulation of the vagina and/or cervix by a glass rod duplicates the abbreviating effects of coitus. Moreover, abbreviation of the receptive period by either coital or mechanical stimulation is independent of the ovary, of the amount of estrogen and progesterone used to induce lordosis, of the pituitary, and of the amount of pituitary hormone injected during estrus. The results suggest that the inhibitory effects of vaginocervical stimulation are purely neurally mediated and hormonal mechanisms are not necessary for the influence of the sensory experience. 36 references. (Author abstract)

065434 Jakoubek, B.; Semiginovsky, B.; Kraus, M.; Erdossova, R. Institute of Physiology, Czechoslovak Academy of Sciences, Budejovicka 1083, Prague, Czechoslovakia The alterations of protein metabolism of the brain cortex induced by anticipation stress and ACTH. *Life Sciences (Oxford).* 9:1169-1179, 1970.

The alterations of protein metabolism of the brain cortex induced by anticipation stress and corticotropin (ACTH) are studied in female rats. The possible relationship between excitation processes and brain protein metabolism is reviewed. Evaluation of results appears to be difficult and to obtain additional information, the brain cortical tissue amino acid uptake changes were investigated in rats expecting painful stimulation (electric shock) or treated with ACTH. A significant decrease of the relative specific activity of proteins were observed both in stressed and in ACTH treated animals. However, this decrease is caused by 2 different mechanisms: by an increase in the specific activity of amino acids in stressed animals; and by a decrease of the specific activity of proteins in ACTH treated animals. The relative specific activity of proteins is the ratio of the specific activity of proteins to the counts (C14) of the trichloroacetic acid soluble fraction. The experiments demonstrate that both stress and ACTH are capable of altering the uptake of amino acids into brain cortical slices, irrespective of underlying mechanism. 20 references.

065470 Sanseigne, Alain. Squibb International, New York, New York Chemistry and pharmacology of fluphenazine decanoate. *Diseases of the Nervous System.* Supplement 31(9):10-11, 1970.

The chemistry and pharmacology of fluphenazine decanoate is reviewed briefly. The lack of understanding of the metabolism and mechanism of action of this important phenothiazine is noted. The results of animal studies, largely based on the most widely used tests -- determination of extent of protection against apomorphine induced emesis in dogs, and induced inhibition of conditioned reponse in rats -- seem to correlate fairly well with human pharmacology. Clinical data is needed to fully clarify the human pharmacology.

065494 Ho, Beng T.; McIsaac, William M.; An, Rong; Harris, Robert T.; Walker, K. E.; Kralik, Patricia M.; Airaksinen, Mauno M. Texas Research Institute of Medical Sciences, 1300 Moursund Avenue, Texas Medical Center, Houston, Texas 77025 Biological activities of some 5-substituted N,N-dimethyltryptamines, alpha-methyltryptamines, and gramines. *Psychopharmacologia (Berlin).* 16(5):385-394, 1970.

Three series of derivatives of N,N-dimethyltryptamine, alpha-methyltryptamine and gramine bearing substitutes of varying electronic nature on the C-5 position were tested for acute toxicity, effect on barbiturate sleeping time, antireserpine effect, swim maze, variable interval conditioned behavior, and inhibition of monoamine oxidase. No correlation could be made between the electronic effects and their pharmacological activities. It was thus suggested that there exist different pharmacological receptors for the tryptamines and gramines. 17 references. (Author abstract)

066186 Villablanca, J.; Schlag, J.; Marcus, R. Catedra de Fisiopatologia, Escuela de Medicina, Universidad de Chile, Santiago, Chile Blocking of experimental spike and wave by a localized forebrain lesion. *Epilepsia.* 11(2):163-177, 1970.

In an experimental inquiry into whether a lesion in the interior thalamic peduncle (ITP) region would also block the cortical spike, the 3/sec spike and wave electrocortical pattern was

produced by electrical stimulation of the midline thalamus in 10 out of 16 cats. In these animals, a unilateral lesion in the area of the inferior thalamic peduncle markedly decreased the homolateral spike and wave complexes and the spontaneous EEG spindle bursts; the blockade was bilateral in two cases with bilateral ITP lesions. In all 12 cats injected with chlorambucil spike and dome electrocortical components were seen; yet these seldom were typical spike and wave complexes. In 6 of these animals, a lesion in the region of the ITP caused a reduction of the cortical action of the drug but this effect was less marked than that upon the electrically produced complex. In 6 cats, some cortical effects of the drug persisted even after complete 'isolation' of the frontal poles. In the cat a lesion in the region of the ITP blocks the electrically produced spike and wave and only reduces the chlorambucil induced electrocortical pattern. At present no particular structure in this region can be designated as responsible for the effect. Chlorambucil produces an atypical spike and wave electrocortical pattern probably by a dual action upon the thalamus and the cortex. It is suggested that the lesion affects only the thalamic component of this action. 24 references. (author abstract modified)

066187 Hardy, Russell W. National Institute of Neurological Diseases and Stroke, National Institutes of Health, Bethesda, Maryland Unit activity in Premarin-induced cortical epileptogenic foci. *Epilepsia.* 11(2):179-186, 1970.

In an examination of the activity of cortical neurons within Premarin foci utilizing 34 adult cats it was discovered that application of Premarin to a relatively wide area of cat cerebral cortex (postsigmoid gyrus), unilaterally or bilaterally, results in the production of epileptogenic foci. Such foci are characterized by interictal paroxysmal activity consisting of surface negative discharges recurring sporadically at variable intervals. In instances of bilateral application of compound, such discharges tend to occur synchronously over the 2 homologous regions. It has not been possible to confirm the alleged property of Premarin to induce 'spike and wave' complexes rhythmically recurring at about 3/seconds. Unit activity during these events consisted of spike bursts with paroxysmal depolarization shifts in correspondence with the surface negative component. No characteristic features were noted in either surface or cellular events: both were closely reminiscent of those seen in other types of experimentally induced epileptogenic foci. 18 reference. (author abstract modified)

066278 Borga, Olof; Hamberger, Bertil; Malmfors, Torbjorn; Sjoqvist, Folke. Department of Histology, Karolinska Institutet, Stockholm, Sweden The role of plasma protein binding in the inhibitory effect of nortriptyline on the neuronal uptake of norepinephrine. *Clinical Pharmacology and Therapeutics.* 11(4):581-588, 1970.

The inhibitory effect of nortriptyline (NT) on the neuronal uptake of radiolabeled norepinephrine (NE) was studied with the use of the rat iris preparation in Krebs-Ringer solution or human plasma. When added to the incubation medium, NT inhibited the uptake of NE approximately ten times as effectively in buffer as in human plasma within the tested concentration range of NT (.00000001 to .000001M). This result is in good agreement with the 94 percent binding (at NT concentration of .0000011M) obtained by the ultrafiltration method. Plasma from patients treated with NT also inhibited the uptake of NE. Correlation between the inhibitory effect and the endogenous plasma level of NT in the 14 patients studied was significant (p less than 0.001). When NT was added in different concentrations to control plasma the inhibitory effect observed was close to that obtained with patient plasma containing the same endogenous concentration of NT. 16 references. (author abstract)

066315 Grelak, R. P.; Clark, R.; Stump, J. M.; Vernier, V. G. E. I. du Pont de Nemours and Co. Inc., Pharmaceuticals Division, Industrial and Biochemicals Department, Wilmington, Delaware Amantadine-dopamine interaction: possible mode of action in parkinsonism. *Science.* 169(3941):203-204, 1970.

Three groups of 6 dogs (5 to 12kg) were anesthetized (sodium barbital, 200mg/kg, and sodium pentobarbital, 15mg/kg, intravenously), and 1 group received 5 intravenous injections of dopamine hydrochloride (0.1mg/kg weight) at 30 minute intervals. Each of the first 4 injections of dopamine was followed 6 or 8 minutes later by amantadine hydrochloride (0.016 to 2.0mg/kg weight, cumulatively, intravenously). The 2 control groups were treated similarly except that 1 group received saline (0.1ml/kg intravenous) instead of dopamine, and the other group received

saline instead of amantadine. Amantadine releases catecholamines from peripheral nerve storage sites, and may have the same action within the central nervous system. This release may account for the reported efficacy of amantadine hydrochloride in thetreatment of human parkinsonism. The catecholamine releasing action of amantadine was enhanced by priming the dogs with dopamine prior to each injection of amantadine. The slight vasopressor response to amantadine alone was probably not due to a direct action upon receptors. The lowest effective intravenous dose of amantadine in dogs primed with dopamine (0.08mg/kg) was well below the oral doses of amantadine used in the treatment of parkinson patients (2 to 3mg/kg). 7 references.

066363 Draskoczy, P. R.; Trendelenburg, U. Department of Pharmacology, Harvard Medical School, Boston, Massachusetts 02115 Intraneuronal and extraneuronal accumulation of sympathomimetic aminesin the isolated nictitating membrane of the cat. ***Journal of Pharmacology and Experimental Therapeutics.*** **174(2):290-306, 1970.**

The accumulation of norepinephrine-H3 (NE-H3) in the isolated normal nictitating membrane of the cat was linearly related to bath concentrations which varied from 0.6ng/ml to 100microgram/ml of dl-NE-H3. Experiments with denervated membranes showed that with low bath concentrations accumulation in the normal membrane was mainly due to intraneuronal accumulation, while extraneuronal accumulation occurred in both normal and denervated membranes when the bath concentration was increased to 1microgram/ml or more of dl-NE-H3. If it is assumed that extraneuronal accumulation is identical in normal and in denervated membranes, intraneuronal accumulation can be calculated as the difference in NE-H3 content between the normal and the denervated membrane. Intraneuronal accumulation was saturable at bath concentrations of about 1 microgram/ml of dl-NE-H3. The sharp increase in the extraneuronal accumulation observed with higher concentrations of dl-NE-H3 in denervated membranes coincided with a pronounced relative decrease in the tissue content of O-methylated metabolites-H3. Intraneuronally retained NE-H3 had a long half-life on wash out, while that of extraneuronally retained NE-H3 was only about 10 minutes. At least some of the norepinephrine which leaves the extraneuronal stores seems to be able to reach the receptors. The two types of accumulation were characterized pharmacologically. Intraneuronal accumulation was reduced by cocaine, phenoxybenzamine or pretreatment with reserpine and not affected by metanephrine, or block of catechol-O-methyltransferase or monoamine oxidase. Extraneuronal accumulation was reduced by metanephrine or phenoxybenzamine, increased after block of catechol-O-methyltransferase or monoamine oxidase and was unaffected by cocaine or pretreatment with reserpine. Relative rates of extraneuronal accumulation were: isoproterenol-H3 greaterthan epinephrine-H3 equals NE-H3. 26 references. (author abstract)

066364 Cabana, Bernard E.; Gessner, Peter K. Pharmacology Department, Bristol Laboratories, Syracuse, New York The kinetics of chloral hydrate metabolism in mice and the effect thereon of ethanol. ***Journal of Pharmacology and Experimental Therapeutics.*** **174(2):260-275, 1970.**

The kinetics of chloral hydrate metabolism after the i.p. administration of this agent were investigated in mice. Chloral hydrate was found to have a biologic half-life in this species of 12.0minutes, the rate constant for its disappearance being 0.057 min. Of the administered chloral hydrate 56% was reduced to trichloroethanol, the rate constant for this process being 0.032 min. Trichloroethanol itself was found to be metabolized much more slowly, the rate constant for its disappearance being 0.0033 min and its biologic half-life in mice 211 minutes. From this data it proved possible to predict quantitatively the degree of accumulation of trichloroethanol in vivo after chloral hydrate administration and to confirm the prediction experimentally. It was observed that in mice trichloroethanol is not oxidized to trichloroacetic acid in any detectable amounts. Trichloroacetic acid formation from chloral hydrate was found to occur with a rate constant of 0.0064 min resulting in the oxidation in this manner of some 11% of the administered chloral hydrate. About 9.6%of the administered chloral hydrate was found to escape metabolism altogether, at least 4.5% of it by excretion into urine. Coadministration of an equimolar amount of ethanol was found to lead to a significant increase in the rate of chloral hydrate disappearance, the rate constant for it under these conditions being 0.075 min. The rate constant for trichloroacetic acid formation did not change significantly under these circumstances although sig-

nificantly less trichloroacetic acid was formed from the administered chloral hydrate. Trichloroethanol formation was the only other process whose rate was increased by coadministration of ethanol, the rate constant under these conditions (0.059 min) being increased by 84%. The rate of trichloroethanol disappearance was found not to be significantly altered by ethanol coadministration. On this basis it was possible to predict quantitatively an even greater accumulation of trichloroethanol in vivo and also to confirm this experimentally. It was also found that after i.v. administration trichloroethanol is 1.18 times as potent as chloral hydrate on a molar basis in causing a loss of righting reflexes. It is concluded that the greater accumulation of trichloroethanol which occurs after coadministration of ethanol can adequately explain the observed potentiation by this agent of the effects of chloral hydrate in mice. 43 references. (author abstract)

066365 Gessner, Peter K.; Cabana, Bernard E. 122 Capen Hall, State University of New York, Buffalo, New York 14214 A study of the interaction of the hypnotic effects and of the toxic effects of chloral hydrate and ethanol. ***Journal of Pharmacology and Experimental Therapeutics.*** **174(2):247-259, 1970.**

The synergism between the hypnotic effects of chloral hydrate and ethanol was investigated in male mice by determination of ED50's and use of the isobolographic method. A significant potentiation of the hypnotic effects was observed for mixtures in which these agents were present in a weight ratio equal to or greater than 1:7.2, simple additivity being observed with weight ratios smaller than 1:7.2. Investigation of the synergism between trichloroethanol, an active metabolite of chloral hydrate, and ethanol and chloral hydrate, respectively, revealed no departures from simple additivity, thus leading to the conclusion that the interaction must be one between chloral hydrate and ethanol directly. The potentiation was also characterized by the observations that mixtures with these compositions also exhibited shorter duration of action for equipotent doses and that administration of the ethanol two minutes prior to the chloral hydrate resulted in a further significant potentiation. Synergism of the toxic effects of chloral hydrate and ethanol was investigated by determination of 24 hour, nonaggregated LD50's. Mixtures of the two agents in the weight ratio 3.6:1 (1:1 molar ratio) revealed significant potentiation, whereas those in the weight ratioof 1:5, 1:10 and 1:15 showed partial but significant antagonism. No departures from simple additivity were seen with mixtures in the weight ratios of 1:1, 1:1.14, 1:3 and 1:30. Therapeutic ratios and standard safety margins for chloral hydrate - ethanol mixtures in the weight ratios of 3.6:1, 1:1 and 1:1.14 were all found to be significantly greater than the respective values for either chloral hydrate or ethanol. 30 references. (author abstract)

066366 Kato, R.; Takahashi, A.; Ohshima, T.; Hosoya, E. Department of Pharmacology, National Institute of Hygienic Sciences, Kamiyoga, Setagaya-ku, Tokyo, 158, Japan Effect of morphine administration on the hydroxylation of steroid hormones by rat liver microsomes. ***Journal of Pharmacology and Experimental Therapeutics.*** **174(2):211-220, 1970.**

The effect of morphine administration on progesterone and testosterone hydroxylation by liver microsomes of male and female rats was investigated. The administration of morphine significantly decreased the content of cytochrome P-450 in male rats, but not infemale rats. Progesterone and testosterone hydroxylation is markedly decreased in morphine treated male rats, but not in the females. In agreement with those results, the magnitude of the spectral changes induced by progesterone and testosterone is decreased only in morphine treated male rats, but not in the females. Castration in male rats decreased the magnitude of spectral changes and hydroxylating activities for progesterone and testosterone, and the administration of testosterone to castrated rats restored these values to the level observed in intact male rats. The magnitude of spectral change and hydroxylating activity for progesterone and testosterone in castrated male rats was not decreased by morphine treatment, but was markedly decreased in testosterone treated castrated rats. Therefore, the ratios of the hydroxylating activity for progesterone and testosterone to the magnitude of the spectral changes are not significantly affected in morphine treated male and female rats. These results indicate that the decrease in the magnitudes of the spectral changes is related to the decrease in the hydroxylation of steroid hormones. The magnitude of spectral change induced by progesterone or testosterone per unit of P-450 content was decreased in morphine treated male rats, but not

in the females. Since the binding capacity of P-450 with progesterone or testosterone is dependent on the action of androgen, an impairment of the action of androgen by morphine is assumed to be a responsible factor. 28 references. (author abstract)

066368 Short, Charles R.; Davis, Lloyd E. Veterinary Physiology and Pharmacology, University of Missouri, Columbia, Missouri 65201 Perinatal development of drug-metabolizing enzyme activity in swine. *Journal of Pharmacology and Experimental Therapeutics.* 174(2):185-196, 1970.

To establish the normal pattern of development of several drug metabolizing systems in swine, three oxidative, one reductive, one hydrolytic and one synthetic mechanism were studied in vitro utilizing preparations of liver and kidney obtained from the pigs at weekly intervals from the 100th day of gestation through the 10th week postpartum. The oxidation of hexobarbital, l-amphetamine, p-nitroanisole and zoxazolamine, the hydrolysis of procaine and the glucuronidation of phenolphthalein occurred at very low rates in the tissues of the fetal and newborn pig, whereas the capacity for azo reduction of Neoprontosil by both tissues was evident at these ages. The postnatal pattern of development in liver appeared to be biphasic in nature, with the greatest rate of increase in activity occurring during the first three to four weeks postpartum for all pathways except azo reduction (four to six weeks). The reductive and hydrolytic mechanisms developed slowly in kidney after birth, whereas the capacity of this organ for oxidative metabolism or for glucuronic acid conjugation was insignificant at all ages. The content of glycogen in the liver at various ages after birth did not correlate well with the development of drug metabolizing enzyme activity over the entire period studied. The CO-binding pigment (cytochrome P-450) of hepatic microsomes developed in parallel with the oxidative and reductive pathways, suggesting that this cytochrome may be rate limiting to the development of these pathways. 29 references. (author abstract modified)

066369 Schnell, Robert C.; Miya, Tom S. CPT/MSC Chemistry Section, 6th U.S. Army Medical Laboratory, Fort Baker, California 94965 Altered absorption of drugs from the rat small intestine by carbonic anhydrase inhibition. *Journal of Pharmacology and Experimental Therapeutics.* 174(2):177-184, 1970.

The absorption of C14-dextroamphetamine sulfate, C14-salicylic acid and C14-urea from in vivo intestinal loops located either in the duodenum or ileum in male rats was determined after pretreatment with acetazolamide. In the ileum, after acetazolamide the absorption of d-amphetamine was decreased, that of salicylic acid was increased and that of urea was unchanged. The pH of the ileal contents was more acidic after acetazolamide. Plasma levels generally reflected the absorption of the respective compound. In the duodenum, after acetazolamide the absorption of d-amphetamine was increased, that of salicylic acid was decreased and that of urea was unchanged. The pH of the duodenal contents was not changed after acetazolamide. Again, plasma levels generally reflected the absorption of the respective compound. Tissue binding of each drug within the two intestinal tissues did not differ after acetazolamide. Carbonic anhydrase assays revealed that the acetazolamide treatment abolished enzyme activity in the intestinal tissue. The differential absorption pattern of the acidic and basic drug from duodenal and ileal sites suggests that the alterations in absorption were secondary physiologic changes resulting from carbonic anhydrase inhibition. 23 references. (author abstract)

066372 Downes, Hall; Williams, John K. Department of Pharmacology, University of Utah College of Medicine, Salt Lake City, Utah 84112 Effects of a convulsant barbiturate on the spinal monosynaptic pathway. *Journal of Pharmacology and Experimental Therapeutics.* 168(2):283-289, 1970.

The effects of convulsant barbiturates on the monosynaptic (2N) reflex was recorded electrically from the seventh lumbar or first sacral ventral roots of 37 unanesthetized spinal cats. In i.v. doses of 0.3to 0.6mg/kg, the convulsant barbiturate, 5-(2-cyclohexylideneethyl)-5-ethyl barbituric acid, produced a prominent increase in the 2N response. Accompanying changes in presynaptic and postsynaptic inhibition did not account adequately for the increase in the 2N response. Pentobarbital Na in low i.v. doses (2mg/kg) produced an increase in the 2N response of lesser extent and duration; after pentobarbital, the effect of the convulsant barbiturate was markedly diminished. The antagonism was reversible, and depression of the 2N response produced by larger doses of pentobarbital was reversed by larger doses of the convulsant barbiturate. 17 references. (author abstract modified)

066374 Sulser, F.; Owens, M. L.; Strada, S. J.; Dingell, J. V. Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37203 Modification by desipramine (DMI) of the availability of norepinephrine released by reserpine in the hypothalamus of the rat in vivo. *Journal of Pharmacology and Experimental Therapeutics.* 168(2):272-282, 1970.

The present investigations were undertaken to determine whether experiments with a push-pull cannula in vivo can furnish information concerning drug induced changes in the availability of adrenergic neurohumors at central adrenergic effector sites and also to determine whether desipramine (DMI) can alter the metabolic fate of catecholamines released by reserpine from intraneuronal storage sites in the brain. After the intraventricular administration of H3-norepinephrine, the radioactivity released into the perfusate from the hypothalamus decreased with time, while the ratio of deaminated-O-methylated catecholamine metabolites to amines (DOM/A) remained constant. Reserpine increased both the radioactivity in the perfusate and the ratio of DOM/A. The amount of unchanged norepinephrine recovered in the perfusate was, however, only slightly reduced, whereas the amount of normetanephrine was markedly decreased. Reserpine did not enhance the release of C14-urea into both norepinephrine and normetanephrine in the perfusate. After pretreatment with DMI, reserpine markedly increased the amounts of both norepinephrine and normetanephrine in the perfusate. Since DMI does not inhibit monoamine oxidase, the findings thus suggest that DMI blocks the reuptake of norepinephrine released by reserpine in brain in vivo by inhibiting the amine transport mechanism in the neuronal membrane. 48 references. (author abstract)

066380 Brosnan, Celia Fildes; Bunge, Mary Bartlett; Murray, Margaret R. Department of Surgery, Columbia University College of Physicians and Surgeons, New York, New York 10032 The response of lysosomes in cultured neurons to chlorpromazine. *Journal of Neuropathology and Experimental Neurology.* 29(3):337-335, 1970.

To explore the relationship between chlorpromazine (CPZ) induced granules of the neuronal cytoplasm to the lysosomal system of the cell CPZ in appropriate concentrations was administered to organized cultures of rat dorsal root ganglia, which were examined by electron microscopy after 1, 4, and 24 hours. A transient abnormal granularity of the cytoplasm visualized with the light microscope during this period is shown by the electron microscope to be due to the formation of large, multilaminated dense bodies within the cytoplasm of neurons and supporting cells. These become prominent within a 4 hour interval after exposure, and at 24 hours have increased considerably in number and size. After the shorter interval they contain vacuoles of cytoplasm. (All cultures recover uneventfully within a few days.)Lysosomal enzyme induction accompanies these changes. Acid phosphatase activity, demonstrated by the Gomori method or an adaptation thereof, is observed in these abnormal dense bodies at 4 hours. At 24 hours reaction product is present in the dense bodies and extensively throughout the somas of neurons which have received the drug at .00007 M; in cultures receiving twice this dose it is diminished at this time. It was concluded here that CPZ is concentrated within the multilaminated dense bodies, which are a part of the lysosomal system of the cell. This pattern of response follows the general course observed in many cell types after exposure to certain vital dyes. 40 references. (author abstract modified)

066382 Frank, G. B., Jhamandas, K. Department of Pharmacology, University of Alberta, Edmonton, Alberta, Canada Effects of general depressant drugs on the electrical responses of isolated slabs of cat's cerebral cortex. *British Journal of Pharmacology (London).* 39(4):707-715, 1970.

The effects of central depressants on neurons in the cerebral cortex and the determination of how closely their effects correspond to the effects of the local and general anesthetic were studied. In the neuronally isolated cortex of the cat, local application of diphenhydramine, promethazine, gammahydroxybutyrate, gammabutyrolactone, gamma aminobutyric acid, hyoscine and pethidine, and the intravenous injection of diazepam and meprobamate depressed or abolished the surface negative and surface positive response to direct stimulation and raised the stimulus threshold of the positive burst response. These effects were the same as previously demonstrated for general and local anesthetics on the same preparation. Chlorpromazine produced a similar depression in small concentrations but caused spontaneous activity in higher concentrations. In contrast to local application, pethidine

when given by intravenous injection in a high dose produced convulsant activity in the isolated cortical slab. The possibility was suggested that the convulsant activity was produced by a metabolite of pethidine. The results of this investigation suggest that the central depression produced by a number of structurally unrelated drugs is indicative of an anesthetic like property of these drugs. 15 references. (author abstract modified)

066386 Rush, M. L.; Pearson, Leonie; Lang, W. J. Department of Pharmacology, University of Melbourne, Parkville, Victoria 3052, Australia Conditional autonomic responses induced in dogs by atropine and morphine. ***European Journal of Pharmacology (Amsterdam).*** **11(1):22-28, 1970.**

Using either atropine or morphine as the unconditional stimulus (UCS) and employing classical conditioning techniques, the establishment of conditional changes of salivation, gastric secretion and heart rate was investigated in dogs. With morphine, 2mg/kg, as the UCS, conditional increases in salivation, gastric secretion and heart rate resulted: these conditional responses were similar to the effects produced by this dose of the drug. A larger dose of morphine, 10mg/kg, produced an initial tachycardia and then a marked secondary bradycardia as the unconditional response. Although the conditional stimulus (CS) was presented during the secondary phase, conditional bradycardia could not be established. With atropine, 0.5mg/kg as the UCS, conditional salivation occurred but no significant conditional changes in gastric secretion or heart rate were observed during 21 pairings of UCS and CS. These results support the view that centrally mediated actions of drugs are more readily conditioned than are peripheral ones. The findings have implications in placebo reaction in the clinical trial of drugs. 21 references. (author abstract)

066411 Berkowitz, Barry A.; Tarver, James H.; Spector, Sydney. Roche Institute of Molecular Biology, Nutley, New Jersey 07110 Release of norepinephrine in the central nervous system by theophylline and caffeine. ***European Journal of Pharmacology (Amsterdam).*** **10(1):64-71, 1970.**

The effect of caffeine and theophylline on the disposition of brain norepinephrine was studied. Neither drug changed the endogenous concentration of norepinephrine in the rat brain following acute or chronic administration. Both lowered the concentration of norepinephrine following inhibition of norepinephrine synthesis with alpha-methyltyrosine or 5-hydroxy-alpha-methyltryptophan. In the guinea pig, caffeine either alone or following blockade of norepinephrine synthesis lowered brainstem norepinephrine levels. Following inhibition of monoamine oxidase in the rat, theophylline and, to a lesser extent, caffeine elevated brainstem norepinephrine levels while theobromine was without effect. Caffeine increased brainstem norepinephrine synthesis in the guinea pig. The data were consistent with the conclusion that caffeine and theophylline can release norepinephrine, and suggest consideration of an adrenergic component in examining their effects. There was no correlation between release of norepinephrine in brain and central nervous systemstimulation. Large or multiple doses of caffeine which, when given alone produced little effect, resulted in marked hyperthermia and increased toxicity when given in combination with a monoamine oxidase inhibitor. 31 references. (author abstract)

066413 Ho, A. K. S.; Loh, H. H.; Craves, F.; Hitzemann, R. J.; Gershon, S. Neuropsychopharmacology Research Unit, Department of Psychiatry and Neurology, New York University Medical Center, New York, New York The effect of prolonged lithium treatment on the synthesis rate and turnover of monoamines in brain regions of rats. ***European Journal of Pharmacology (Amsterdam).*** **10(1):72-78, 1970.**

The effect of prolonged lithium treatment on the state levels and turnover rates of serotonin, norepinephrine and dopamine was studied in the cerebral cortex, cerebellum, diencephalon, brain stem and hypothalamus. In normal animals all 3 monoamines showed significant differences in the steady state levels and turnover rates among brain regions. The highest and lowest rates of synthesis of both serotonin and norepinephrine were found in the hypothalamus and cerebellum, respectively, while the rate of synthesis of dopamine was highest in the diencephalon and lowest in the cerebellum. Prolonged lithium treatment produced a significant change in serotonin levels only in the hypothalamus (46% reduction) and brain stem (26% reduction) but no significant change in the other region (no significant alteration in norepinephrine or dopamine levels occurred). In regional studies, the cerebellum showed a 37%increase in the synthesis rate, whereas the

hypothalamus showed a 51.1% reduction. The turnover rates of norepinephrine and dopamine were not significantly affected. A variable relationship between the tissue concentration and synthesis rates of the monoamines under both normal conditions and lithium treatment may exist, observed differences being related to the morphology of these discrete areas. 27 references. (author abstract modified)

066468 Allison, Truett; Van Twyver, Henry. Veterans Administration Hospital, West Haven, Connecticut Sensory representation in the neocortex of the mole, Scalopus aquaticus. ***Experimental Neurology.*** **27(3):554-563, 1970.**

The neocortex of 9 moles, Scalopus aquaticus, was explored by the evoked potential technique to determine visual, somatic, and auditory areas comparing sodium pentobarbital with chloralose.No visual evoked response could be recorded in any animal. In agreement with anatomical studies, we conclude that there is essentially no visual cortex in the mole. The primary somatic area appears to have shifted posterolaterally, compared to another insectivore, the hedgehog, possibly due to the absence of visual cortex. The auditory area in the mole is similar in location to that in hedgehog and rat. 16 references. (author abstract modified)

066474 Ranck, James B., Jr. Department of Physiology, University of Michigan, Ann Arbor, Michigan 48104 Electrical impedance changes in many sites of brain in paradoxical sleep, anesthesia and activity. ***Experimental Neurology.*** **27(3):454-475, 1970.**

Impedance changes in relation to spontaneous behavior and various brain regions were studied. The electrical impedance of a part of brain approximately 1 mm in dimension was measured with a four electrode, very low current method in 61 male rats. The testing frequency was usually 1000 Hz, and only the magnitude of impedance was measured. Impedance increased in paradoxical sleep in 42 of the 61 sites and decreased at three sites in the pons. The greatest changes were in subiculum and presubiculum with changes usually more than 10% and up to 25 to 30%. Intermediate changes of 2 to 10% were found in parasubiculum and entorhinal cortex. Most other changes were less than 4%, and there is a suggestion of greater changes in the pretectal area. All sites with changes greater than 4% were within 1 mm of a pial or ependymal surface. During anesthesia with pentobarbital in 23 rats impedance increased in 2, 8 showed no change, and 13 decreased. During unrestrained spontaneous activity in a small familiar cage the impedance usually became either more variable or decreased generally to a maximum of 1 to 10%, or both, but at a single site the response was not always the same. No tests beyond simple observation were used, and with this limited basis no clearer relation of impedance to behavior than simply to motor activity was apparent. In a change from quiet arousal to slow wave sleep, or vice versa, there were no impedance changes. But at all sites activity usually had an effect. This was particularly marked in entorhinal cortex - parasubiculum and brain stem. Almost no impedance changes were seen other than of these three types. Impedance changes in brain are thus widespread and occur frequently in the usual behavior of rats. These results generally corroborate and expand the results of the Adey-Kado group with a different method with some advantages. 31 references. (author abstract modified)

066497 Nishie, K.; Waiss, A. C.; Keyl, A. C. Western Regional Research Laboratory Agricultural Research Service, U.S. Department of Agriculture, Albany, California 94701 Pharmacology of alkyl and hydroxyalkylpyrazines. ***Toxicology and Applied Pharmacology.*** **17(1):244-249, 1970.**

The following byproducts formed in the ammoniation of glucose were studied pharmacologically: pyrazine; 2-methylpyrazine; 2 -hydroxymethylpyrazine; 2,3-dimethylpyrazine; 2,5-dimethylpyrazine; 2,6-dimethylpyrazine; 2-hydroxy-5-methylpyrazine; 2-methyl-5 -arabotetrahydroxybutylpyrazine; 2-methyl-6-arabotetrahydroxybutylpyrazine; 4(5)-methylimidazole (4-me-I); 4-hydroxymethylimidazole; and 4 - arabotetrahydroxybutylimidazole. Of these and other byproducts, only 4-me-I had convulsant activity and the ability to induce in laboratory animals the signs observed in cattle fed toxic ammoniated molasses. Other derivatives of imidazole (hydroxymethyl and arabotetrahydroxybutyl) were pharmacologically inactive at a dose of 2g/kg in mice. With the exception of 4-me-I, all compounds in this series were relatively nontoxic. Mono-methylpyrazines and dimethylpyrazines showed weak central nervous depressant activity (hypnotic and anticonvulsant). 2,3-Dimethylpyrazine was the most potent in this regard, but

had only approximately 1/13 of the hypnotic activity of phenobarbital sodium and 1/21 of the anticonvulsant potency of phenobarbital against 4-me-I-induced seizures. Pyrazines with either OH, CH2OH or --(CHOH)3--CH2OH substituents were inactive as hypnotics and anticonvulsants and, in addition, were relatively nontoxic. 18 references. (author abstract)

066498 Reinhard, John F.; Spector, Elliot. Department of Pharmacology, Graduate School of Pharmaceutical Sciences, Northeastern University, Boston, Massachusetts 02115 Effects of phenobarbital, phenylbutazone, 3,4-benzpyrene, or 3-methylcholanthrene on ethanol metabolism in the rat. *Toxicology and Applied Pharmacology.* 17(1):12-22, 1970.

The effects of phenobarbital, phenybutazone, 3,4-benzprene, or 3-methylcholanthrene on ethanol metabolism in the rat was studied. It was found that repeated daily administration of phenobarbital (38, 76 and 150mg/kg/day for 3 days) or 3-methylcholanthrene (125mg/kg/day for 3 days), agents known to activate hepatic microsomal enzyme systems, produced significant acceleration of the rate of ethanol metabolism as shown directly by using liver homogenates, and indirectly by demonstrating antagonism of the hypnotic and toxic effects of ethanol in intact animals. The carcinogen 3,4-benzpyrene (25mg/kg/day for 3 days), also known to activate microsomal enzymes, reduced ethanol sleeping time and toxicity significantly, yet failed to accelerate ethanol metabolism in vitro. Another enzyme inducer, phenylbutazone (125mg/kg/ day for 3 days), was inactive by both direct and indirect procedures. Presumably ethyl alcohol dehydrogenase was 'activated' by phenobarbital and 3-methylcholanthrene in the in vitro studies. Sleeping times and toxicity were significantly reduced in the drug pretreated, as compared to control, animals, yet plasma concentrations of ethanol were virtually identical in the two groups. It is concluded that some mechanism other than increased ethanol metabolism was responsible for the reduced sleeping time and lowered toxicity. This might involve reduced sensitivity of brain cells or altered permeability of the cell membranes to ethanol. 7 references. (author abstract modified)

066499 Haggendal, Jan; Dahlstrom, Annica. Department of Pharmacology, University of Goteborg, Goteborg, Sweden Uptake and retention of 3H-noradrenaline in adrenergic nerve terminals after reserpine and axotomy. *European Journal of Pharmacology (Amsterdam).* 10(3):411-415, 1970.

The recovery time for the adrenergic neuron to take up and retain 3H-noradrenaline (NA) after reserpine treatment was studied using the gastrocnemius muscle and submaxillary gland of male rats (200 to 250g). Reserpine (10mg/kg, i.p.)was given 18, 24, 36 and 48 hours prior to sacrifice and unilateral ligation of sciatic nerve or unilateral removal of superior cervical ganglion performed. Tritiated noradrenaline (2.5or 5mcg/kg, i.v.)was administered 30 minutes before death. Sciatic nerve ligation led to initially low levels of NA in muscles on both sides, although by 36 and 48 hours considerably higher levels were found on the intact side. Submaxillary gland results closely correlated with those from gastrocnemius muscle. An axoplasmic downflow of newly formed storage granules is probably essential for the recovery processes after reserpine treatment.

066500 Samanin, R.; Gumulka, W.; Valzelli, L. Istituto di Ricerche Farmacologiche 'Mario Negri', Via Eritrea, 62, 20157, Milan, Italy Reduced effect of morphine in midbrain raphe lesioned rats. *European Journal of Pharmacology (Amsterdam).* 10(3):339-343, 1970.

Lesions of the midbrain raphe were performed in female rats (180g) to study the role of brain 5-hydroxytryptamine (5-HT) in morphine analgesia. Analgesic activity of morphine was tested by placing the animals on a 55 degree C hot plate 30 minutes before and 30, 60 and 90 minutes after morphine administration (12mg/kg, s.c.), by compression of the tail until vocalization was evoked and by s.c. electrical stimulation. Lesions of the midbrain raphe decreased forebrain serotonin by 79% and the analgesic effects of morphine were considerably reduced versus control animals using the three parameters noted above. A group of rats with lesions lateral to the midbrain raphe showed no change in forebrain serotonin and gave similar experimental results to the sham operated rats. 30 references.

066501 Iversen, L. L. Department of Pharmacology, University of Cambridge, Cambridge, England Inhibition of catecholamine uptake by 6-hydroxydopamine in rat brain. *European Journal of Pharmacology (Amsterdam).* 10(3):408-410, 1970.

The study was undertaken in an attempt to show whether 6-hydroxydopamine (6-OHDA) has selective affinity for catecholamine uptake sites in rat brain. Uptake of 3H-noradrenaline (NA), 3H-GABA and 3H-hydroxytryptamine was measured in slices of rat hypothalamus and striatum and 6-OHDA was added just before addition of labeled substrate. 6-OHDA was found to have no significant effect on uptake (tissue : medium ratio) of GABA (33.0) or 5-HT (8.2) when compared to control values (34.5and 8.5). Inhibition of NA both in hypothalamus (2.7) and striatum (10.4) was noted, however, in comparison with control values (4.7and 15.2). The findings that 6-OHDA has higher affinity for noradrenergic neurons may explain its greater effectiveness in depleting brain NA than dopamine. 10 references.

066502 Nyback, Henrik; Schubert, Johan; Sedvall, Goran. Departments of Pharmacology and Psychiatry, Karolinska Institutet, S-104 01 Stockholm, Sweden Effect of apomorphine and pimozide on synthesis and turnover of labelled catecholamines in mouse brain. ***Journal of Pharmacy and Pharmacology (London).*** **22(8):622-624, 1970.**

The effect of apomorphine and pimozide on catecholamine accumulation and disappearance in mouse brain was investigated using labeled tyrosine. Saline or the drugs were administered two hours after intravenous injection of C14 tyrosine (10mcC/animal), the animals killed two or seven hours later and brain tyrosine, dopamine and norepinephrine were measured. Apomorphine was found to reduce endogenous norepinephrine to 70% of control values, whereas tyrosine (16mcg/g) and dopamine (0.62mcg/g) were similar to control values (17mcg/g and 0.59mcg/g, respectively). Pimozide exerted a depressant effect only on dopamine levels (0.50mcg/g). Apomorphine was found to depress while pimozide accelerated C14 dopamine disappearance rate and neither drug had an effect on labeled norepinephrine disappearance. The opposite effects of apomorphine and pimozide on brain dopamine metabolism appear to correlate with the opposing effects of these drugs on stereotyped behavior in rats.

066506 Ablad, Bengt; Ek, Lars; Johansson, Borje; Waldeck, Bertil. Department of Pharmacology, AB Hassle, Goteborg, Sweden Inhibitory effect of propranolol on the vasoconstrictor response to sympathetic nerve stimulation. ***Journal of Pharmacy and Pharmacology (London).*** **22(8):627-628, 1970.**

The effects of propranolol on the vasoconstrictor response to peripheral sympathetic nerve stimulation and to norepinephrine was studied in the hind limb of the cat. Sympathetic nerves were stimulated for 90 seconds with impulses of supramaximal voltage at a frequency of 1 to 2/sec, causing a 50 to 80mm Hg increase in femoral arterial pressure. Intraarterial injections of norepinephrine (0.25 to 1mcg) also increased pressure by 50 to 80mm Hg. Propranolol injections (0.1mg/kg, i.v.)were alternated with the nervous or chemical stimulation. Sympathetic nerve stimulation responses were reduced by 14%, whereas the response to norepinephrine was slightly increased (6%). After 0.5mg/kg propranolol, the pressure response to norepinephrine increased by 20%, while the nervous response decreased by 5%.

066507 Fuller, Ray W.; Hines, C. W. Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana Inhibition by p-chloramphetamine of the conversion of 5-hydroxytryptamine to 5-hydroxyindoleacetic acid in rat brain. ***Journal of Pharmacy and Pharmacology (London).*** **22(8):634-635, 1970.**

The metabolism of 3H-5-hydroxytryptamine (5-HT) formed from 3H-5-hydroxytryptophan (5-HTP) was studied in rat brains after administration of p-chloramphetamine (PCA), an agent which lowers 5-HT in rat brain. PCA was injected (20.6mg/kg, i.p.)into male rats (150g) followed 16 hours later by injection of 3H-5-HTP (0.33mC/kg). The animals were sacrified 1, 2 or 4 hours later and their brains were examined for 5-HTP, 5-HT and 5-hydroxyindoleacetic acid (5-HIAA). Radioactivity levels present in 5-HTP and 5-HT were alike in both control and PCA-treated rats, although the amount of radioactivity present as 5-HIAA was markedly decreased. The results suggest that inhibition of monoamine oxidase can occur in PCA-treated rats or can inhibit tryptophan hydroxylation and thus inhibit 5-HT synthesis. 7 references.

066508 Svensson, T. H.; Stromberg, U. Department of Pharmacology, University of Goteborg, Goteborg, Sweden Potentiation by amantadine hydrochloride of L-dopa induced effects in mice. ***Journal of Pharmacy and Pharmacology (London).*** **22(8):639-640, 1970.**

The effects of amantadine hydrochloride on L-dopa-induced responses on motor activity and gross behavior in mice were studied. Female mice

received L-dopa (75 to 1000mg/kg, i.p.)with experimental animals receiving amantadine (100mg/kg) 95 minutes before L-dopa administration. Motor activity was recorded by means of activity meters. Amantadine was not found to exert an effect on motor activity, although potentiation of L-dopa motility effects did occur as well as potentiation of peripheral L-dopa effects. It appears unlikely that amantadine acts by inhibiting dopa decarboxylase in the peripheral sympathetic nervous system. 7 references.

066509 Bowers, M. B., Jr.; Rozitis, A. Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut Acetylcholine release from cortical brain slices of rats injected with lithium. ***Journal of Pharmacy and Pharmacology (London).*** **22(8):647, 1970.**

Measurement of endogenous acetylcholine from electrically stimulated cortical brain slices in rats was studied to determine the effects of lithium on acetylcholine release from brain tissue. Male rats (150 to 200 g) were injected with lithium (2.5mEq/L) or with saline i.p.,b.i.d. for 4 days. After sacrifice, the cortical slices were incubated in Tyrode solution and mounted for electrical stimulation. Acetylcholine levels (0.92) in lithium treated rats were found to be similar to the saline injected controls (0.86). The results do not support the hypothesis that lithium decreases acetylcholine release in mammalian brain. 3 references.

066510 Smith, A.; Hayashida, K.; Kim, Y. Departments of Anesthesiology and Pharmacology, New York Medical College, New York Inhibition by propranolol of ethanol-induced narcosis. ***Journal of Pharmacy and Pharmacology (London).*** **22(8):644-645, 1970.**

The influence of propranolol on the depressant effect of ethanol is the subject of this study. Propranolol (1mg/kg, i.p.)was injected 15 minutes prior to ethanol (25%) administration or sodium pentobarbitone (60mg/kg). Righting reflex time after pentobarbitone was increased by propranolol, but shortened by low doses of propranolol after ethanol administration. Propranolol inhibition of the central depressant actions of ethanol suggests that brain norepinephrine may modulate the depressive response to ethanol. In addition, propranolol was found to be more effective against ethanol depression than against methanol or propano - induced depression. 5 references.

066713 Ancill, R. J.; Harston, S. J.; Neubauer, H.; Redfern, P. H. Pharmacology Group, Bath University, Bath, England The effect of serum from acute schizophrenic patients on rabbit brain amines. ***Archives Internationales de Pharmacodynamie et de Therapie (Gand).*** **186:255-260, 1970.**

Serum from acute schizophrenic and from normal subjects was injected intravenously into 2 groups of rabbits to determine the effect of the serum in brain amines in the rabbits. One hour after injection, the animals were killed and concentrations of 5-hydroxytryptamine, noradrenaline and dopamine were estimated in cerebral hemispheres, cerebellum and the rest of the brain. No significant differences in amine concentrations were found between the 2 groups. 12 references. (Author abstract modified)

066805 Bartonicek, V. J. Sanct Lars Hospital, Lund, Sweden Monoamine oxidase inhibitors, combined with thymoleptics: are they really unusable for human beings. ***Pharmacology.*** **4(2):80-90, 1970.**

Results are presented from trials performed with rats in which monoamine oxidase inhibitors were combined with thymoleptic drugs, a combination formerly used in human beings to treat depressive illnesses. The intensity of yellow fluorescence corresponding to 5 hydroxytryptamine in brain stem of animals given diverse monoamine oxidase (MAO) inhibitors plus thymoleptics (imipramine or desmethylimipramine) was markedly lower than that observed in animals given MAO inhibitor alone. It was, however, higher than that obtained in animals treated with thymoleptic drug alone. The structures containing yellow fluorescent nerve cell bodies in the nucl. raphes pontis showed the nearly uniform decrease of intensity without obvious local differences in the present structures. The employed relative dosage of both inhibitors and thymoleptics was enormous as compared with that customarily used in humans. Only 2 rats died spontaneously out of 64, which is in sharp contrast to fatal accidents observed in humans. The possible explanation of the increased 5 hydroxytrptamine in the neurons is put forward. 24 references. (Author abstract modified)

066822 Mellerup, E. T.; Thomsen, H. Gronlund; Plenge, P.; Rafaelsen, O. J. Psychochemistry Institute, University Department of Psychiatry, Rigshospitalet, Copenhagen, Denmark Lithium effect on plasma glucagon, liver phosphorylase-a and

liver glycogen in rats. Journal of Psychiatric Research (London). 8:37-42, 1970.

The action of lithium on liver glycogen is investigated by studying the effect of lithium on liver phosphorylase-a and on the concentration of immunoassayable glucagon in plasma, and the effect of site of injection of the drug. It was found that intraperitoneal injection of lithium chloride to rats increased radioimmunoassayable glucagon-like substance in plasma and liver phosphorylase-a activity and decreased liver glycogen. Intracisternal injection of lithium chloride was without effect. Intraperitoneal injection of beryllium sulphate decreased liver glycogen but was without effect on plasma glucagon. These findings suggest that the glycogen depletion of the liver induced by lithium is caused by an increase in the secretation of glucagon. The mechanism did not seem to involve a central mediation. 16 references. (Author abstract modified)

066853 Bogan, James. Department of Veterinary Pharmacology, University of Glasgow, Glasgow, Scotland Effect of SKF 525A on the fate of thiopentone. ***Journal of Pharmacy and Pharmacology (London).*** **22(9):709-710, 1970.**

The effect of SKF-525A (beta-diethylaminodiphenylpropyl acetate) on thiopentone blood concentrations and on thiopentone sleeping times was measured on 5 dogs to demonstrate the contribution of hepatic metabolism in the termination of the anesthetic action of thiopentone. SKF-525A was given intravenously (10mg/microgram) 30 minutes before 30mg/kg thiopentone. No alteration in the rate of decline of thiopentone blood levels resulted. In a second experiment, hooded inbred rats were injected intraperitoneally with SKF-525A (10mg/kg) 30 minutes before thiopentone, and a control group was given saline. The sleeping times following injection with thiopentone (25mg/kg) were measured. SKF-525A did not produce any significant difference in thiopentone sleeping times in rats compared with animals given thiopentone alone. These results indicated that hepatic metabolism is not important in the termination of the anesthetic action of thiopentone. 11 references.

066854 Goldstein, Menek; Freedman, Lewis S.; Backstrom, Tony. Department of Psychiatry, New York University Medical Center, Neurochemistry Laboratory, New York, New York 10016 The inhibition of catecholamine biosynthesis by apomorphine. ***Journal of Pharmacy and Pharmacology (London).*** **22(9):715-717, 1970.**

The effects of apomorphine on tyrosine hydroxylase activity and on dopamine biosynthesis was investigated in vitro and in vivo. Sliced rat striata were incubated with C14-catecholamines 30 minutes following treatment of the live animal with 25mg/kg apomorphine given subcutaneously. Haloperidol (2mg/kg intraperitoneally) was given 30 minutes before the apomorphine. Apomorphine inhibited tyrosine hydroxylase activity at concentrations of 0.0001 molar, but not at 0.000001 molar. The biosynthesis of C14-dopamine from C14-tyrosine was inhibited by apomorphine concentrations as low as 0.0000001 molar. Addition of haloperidol to the incubation medium did not affect this inhibitory action. In separate experiments, treatment with apomorphine resulted in a 50% decrease of C14-catecholamine biosynthesis from C14-tyrosine in the telencephalon and in the brain stem of rats. The in vivo inhibitory activity of apomorphine was not affected by pretreatment of the rats with haloperidol. The inhibition of catecholamine biosynthesis by apomorphine may limit the usefulness of this drug or of some apomorphine type derivatives in the treatment of parkinsonism. 9 references.

066937 Curry, S. H.; Derr, J. E.; Maling, H. M. Department of Pharmacology and Therapeutics, London Hospital Medical College, Turner Street, London, E.1, England The physiological disposition of chlorpromazine in the rat and dog. ***Proceedings of the Society for Experimental Biology and Medicine.*** **134(1):314-318, 1970.**

Chlorpromazine (10mg/kg) was rapidly absorbed after intraperitoneal administration in male Sprague-Dawley rats. Concentrations in liver and brain greatly exceeded plasma levels. Chlorpromazine and its metabolites rapidly disappeared from plasma and vascular tissues. In male beagles, chlorpromazine levels in plasma were approximately proportional to the dose during the first 7 hrs after intravenous administration of 3 different doses (1, 3 and 10mg/kg), all in the range commonly used in pharmacological studies. The data suggest that chlorpromazine and its metabolites distribute largely by reversible processes between plasma and tissues. This justifies using plasma concentrations in man as indicators of tissue concentrations. 11 references. (author abstract modified)

066938 Tyce, Gertrude M.; Flock, Eunice V.; Taylor, William F.; Owen, Charles A., Jr. Mayo Clinic and Mayo Foundation, Section of Biochemistry and of Medical Statistics, Rochester, Minnesota 55901 Effect of ethanol on 5-hydroxytryptamine turnover in rat brain. *Proceedings of the Society for Experimental Biology and Medicine.* 134(1):40-44, 1970.

Concentrations of 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) in the brains of Sprague-Dawley rats which had received intoxicating doses of alcohol did not differ from concentrations in brains of control animals. The turnover of cerebral 5-HT was determined from rates of increase in concentration of 5-HT or of decrease in concentration of 5-HIAA after administration of a monoamine oxidase inhibitor (pargyline). Cerebral 5-HT turnover was slightly decreased during ethanol intoxication. 21 references. (author abstract)

066955 Miller, K. W.; Freeman, J. J.; Dingell, J. V.; Sulser, F. Psychopharmacology Research Center, Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37203 On the mechanism of amphetamine potentiation by iprindole. *Experientia (Basel).* 26(8):863-864, 1970.

Male Sprague-Dawley rats were pretreated with either 10mg/kg or 2mg/kg of iprindole 30 minutes before treatment with 2mg/kg of d-amphetamine, and psychomotor stimulation was measured in Williamson activity cages over a period of 10 hours. Either dose of iprindole enhanced and prolonged the psychomotor stimulation elicited by amphetamine for as long as 9 hours. Iprindole alone, at a dose of 10mg/kg caused no increase in psychomotor activity, and d-amphetamine alone, at 2mg/kg, elicited increased psychomotor activity which reached a peak at 1 hour and lasted only 2 hours. Pretreatment with iprindole resulted in a sustained increase in brain levels and a marked increase in body levels of labeled d-amphetamine. Iprindole may act like desipramine, and other tricyclic antidepressants to inhibit the metabolism of d-amphetamine in vivo, without blocking the uptake of norepinephrine in central nerve fibers. 16 references.

067072 Nistico, Giuseppe; Preziosi, Paolo. Institute of Psychiatry, De Crespigny Park, Denmark Hill, London S.E.5, England Contraceptives, brain serotonin, and liver tryptophan pyrrolase. *Lancet (London).* No. 7665:213, 1970.

In a letter to the editor, it was reported that brain levels of 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA), plasma corticosterone, and liver tryptophan pyrrolase were determined in female rats given 416 micrograms/kg norethynodrel and 16.6micrograms/kg mestranol i.m. daily for 10, 20, 30, and 60 days. Controls received no treatment. There was a significant fall in 5-HT after 10 days treatment but almost normal values after 20, 30, and 60 days treatment. Plasma corticosterone and liver tryptophan pyrrolase were increased after 10 days treatment but returned to normal values with continuing treatment. The reduction in 5-HT in the brain possibly resulted from a decrease in tryptophan uptake by the brain induced by kynurenine and other metabolites formed by the action of tryptophan pyrrolase. 16 references.

067081 Ho, Beng T.; Fritchie, G. Edward; Idanpaan-Heikkila, J. E.; Tansey, L. Wayne; McIsaac, William M. Texas Research Institute of Mental Sciences, Houston, Texas 77025 (3H)Harmaline distribution in monkey brain; pharmacological and autoradiographic study. *Brain Research (Amsterdam).* 22(3):397-401, 1970.

Tritium labeled harmaline (20mg/kg, 3.8mC/kg i.v.)distribution in 7 squirrel monkey brains was investigated pharmacologically and autoradiographically. Pronounced tremors and tonic convulsions, followed toward the end of the attack by clonic convulsions in rapid succession were observed within the first few minutes after injection. About 30 minutes after injection, head twitching was observed and it continued for about 2 hours. Lethargy, weakness and incoordination were still apparent after 2 hours, lasting until 4 hours after injection. The cortex accumulated a much higher radioactivity than the white matter, except for a slightly higher concentration in the frontal area. High radioactivity also appeared in the hippocampus, caudate nucleus, putamen, cerebellum, fastigal nucleus and dentate nucleus. At 1 hour the radioactivity was almost evenly distributed throughout the brain. The hippocampus was still relatively high in concentration. A reversal in distribution between white and grey was noted at 4 hours. Shortly after the administration of (3H)harmaline, the distribution of radioactivity at 15 minutes was higher in grey than in white matter. At this early period the plasma level of (3H)harmaline had already dropped to a very low level, one-fourth of the cerebrospinal fluid and one eighth of the frontal cortex. There apparently is a

relation between the anatomical distribution and action of harmaline as reported previously for another hallucinogenic compound. 15 references.

04 MECHANISM OF ACTION - BEHAVIORAL

064749 McKearney, James W. Worcester Foundation for Experimental Biology, 222 Maple Ave., Shrewsbury, Mass. 01545 Rate-dependent effects of drugs: modification by discriminative stimuli of the effects of amobarbital on schedule-controlled behavior. *Journal of the Experimental Analysis of Behavior.* 14(2):167-175, 1970.

A description is given of the effect of nonnoxious stimuli in changing the effect of a drug at a given rate of responding. In the present experiments, the dependence of the effects of amobarbital on control response rate, and changes in this dependency as a result of introduction of various types of discriminative stimuli, are explored. It was shown that, even under conditions where responding under strong stimulus control is enhanced markedly less than responding not under such control, the increases in responding that do occur are inversely related to control response rates. 14 references.

064968 Cole, Sherwood O. Rutgers University, South Jersey Campus, Camden, New Jersey 08102 Experimental effects of amphetamine: supplementary report. *Perceptual and Motor Skills.* 31(1):223-232, 1970.

As a supplement to a previous review, generalizations related to the experimental effects of amphetamine on food motivated operant behavior, bodily activity and avoidance conditioning in rats and mice are evaluated in terms of recent evidence. Acceptance of generalizations related to the drug's action on such behaviors requires that one also accept numerous qualifications or limitations in terms of drug dose factors, S variables, and task characateristics. However, the desirability of such generalizations is stressed. 64 references. (Author abstract)n

065070 Amit, Zalman; Baum, Morrie. McGill University, Montreal, Canada Comment on the increased resistance-to-extinction of an avoidance response induced by certain drugs. *Psychological Reports.* 27(1):310, 1970.

The increased resistance to extinction of an avoidance response induced by certain drugs is analyzed. It is suggested that the experience of being in a drug state for a pharmacologically naive S is aversive and thus acts to increase fear in the avoidance situation. It is possible that the aversion resulting from the drug state, or to put it another way, the fear induced by being drugged, compounded the aversion of the avoidance situation and resulted in increased resistance of extinction of the avoidance response. The interpretation would lead to the prediction that Ss which were previously habituated to the drug state would not exhibit increased resistance to extinction of an avoidance response following drug administration. The habituation could be achieved by exposing the animal to repeated intragastric infusion of the drug or by repeated introperitoneal injections of the drug. 3 references.

065419 Jonason, Kim R.; Lauber, Susan M.; Robbins, Mollie J.; Meyer, Patricia M.; Meyer, Donald R. Ohio State University Research Center, Area 2, 1314 Kinnear Road, Columbus, Ohio 43212 Effects of amphetamine upon relearning pattern and black-white discriminations following neocortical lesions in rats. *Journal of Comparative and Physiological Psychology.* 73(1):47-55, 1970.

Rats which previously had been trained to perform either a pattern or a black white discrimination were subjected to either bilateral anterior or bilateral posterior neocortical lesions, and then retrained on the task while being treated with 1 mg/kg dl-emphetamine sulfate. Amphetamine did not reinstate visual contour perception in rats with posterior ablations, nor did it have any consequence, postoperatively, upon learning or relearning the black white discrimination for rats with anterior neocortical lesions. When a comparison was made between a large group of amphetamine treated rats with posterior ablations and a large group of posteriorly decorticated control rats, a small but consistent tendency toward improved performance was found in the amphetamine injected animals. It was also noted that normal learning scores did not predict either anterior or posterior postoperative retention of the black white discrimination. 8 references. (Author abstract)

065420 Glick, Stanley D.; Levin, Bruce; Jarvik, M. E. Department of Pharmacology, Albert Einstein College of Medicine, Yeshiva University, 1300 Morris Park Ave., Bronx, N. Y. 10461 Role of monkeys' spatial preferences in performance of a nonspatial task. *Journal of Comparative and Physiological Psychology.* 73(1):56-61, 1970.

The performance of monkeys on a nonspatial delayed matching task was analyzed in terms of spatial and color preferences and perseverations. Monkeys were found to utilize significant spatial but not color tendencies. The strength of spatial tendencies was determined to be an important error factor accounting for differences among monkeys in overall accuracy. Spatial tendencies, however, could not account for intrasubject differences in accuracy as a function of testing conditions. Administration of d-amphetamine, scopolamine, and chlorpromazine lowered accuracy. Only the effect of d-amphetamine, however, could be largely attributed to an influence on spatial tendencies. The elicitation of spatial tendencies was found to be somewhat related to the immediacy with which monkeys performed the matching response. 12 references. (Author abstract)

065440 Morrison, Cathleen F.; Stephenson, Jane A. Tobacco Research Council Laboratories, Otley Road, Harrogate, Yorkshire, England Drug effects on a measure of unconditioned avoidance in the rat. *Psychopharmacologia (Berlin).* 18(2):133-143, 1970.

The effects of various drugs in unconditioned avoidance in the rat as measured by exploration of a Y-maze are reported. Rats tend to avoid the elevated, open-sided arm of a Montgomery Y-maze in which the other 2 arms are enclosed by walls. Minor tranquillizers and barbiturates reduce avoidance of the open-sided arm and increase total activity. Chlorpromazine does not affect avoidance. Amphetamine and nicotine reduce high and increase low avoidance levels. 9 references. (Author abstract modified)

065441 Desi, I.; Kertai, P.; Farkas, I.; Musko, Zs.; Hajos, P. Neuropathophysiological Laboratory, Institute of Pathophysiology, University Medical School Budapest, Budapest IX, Hogyes E. 9/Hungary The process of learning in rats undergoing prolonged treatment with psychotropic agents. *Psychopharmacologia (Berlin).* 18(2):144-153, 1970.

The effect of prolonged treatment with amphetamine and chlorpromazine on the process of learning and the change in performance of acquired skills in rats was studied. Maze tests were continued for 23 days and conditioned reflex tests for 37 days. Animals received 0.5mg/kg/day of amphetamine or 0.5mg/kg/day of chlorpromazine added to the drinking water. Further groups received daily intraperitoneal injections of 0.25mg/kg of amphetamine or 4mg/kg of chlorpromazine. The learning index deteriorated initially by oral administration of amphetamine, but subsequently improved, whereas intraperitoneal treatment caused a slight deterioration. Both agents interfered with previously acquired conditioned responses. The frequency of pseudopositive responses was considerably higher following administration of amphetamine, but was unalterated by chlorpromazine. 9 references. (Author abstract modified)

065442 Rohte, Oskar. Research Laboratories, AB Leo, S-25242 Helsingborg, Sweden Observation of the grooming behavior of reserpinized white mice as a method for investigating reserpine antagonism and synergism. *Psychopharmacologia (Berlin).* 18(2):154-161, 1970.

Observations are made of the grooming behavior of reserpinized white mice as a method of investigating reserpine antagonism and reserpine synergism. The grooming movements of reserpinized white mice, dusted with pulverized charcoal, were studied under the influence of psychotropic drugs. With the help of this test it is possible to show differences in the antireserpine properties of different psychotropic substances. Only d-amphetamine, desipramine and Leo 640 (chopramine, a new potential antidepressive) showed positive results in this test and stimulated the grooming movements again. In order to find the position of this new test in the test battery the results were compared with those obtained in the reserpine - temperature and the ptosis tests for mice. 10 references. (Author abstract modified)

065451 Chisholm, Drake C.; Moore, John W. Department of Psychology, University of Massachusetts, Amherst, Massachusetts 01002 Effects of chlordiazepoxide on discriminative fear conditioning and shuttle avoidance performance in the rabbit. *Psychopharmacologia (Berlin).* 18(2):162-171, 1970.

The effects of chlordiazepoxide on discriminative fear conditioning and shuttle avoidance performance in the rabbit are determined. The results of the study show that previously acquired shuttle avoidance performance in rabbits was reduced by chlordiazepoxide. Other animals were given chlordiazepoxide during differential tone -shock pairings. The effects of this differential Pavlovian fear conditioning were tested during extinction, when the tonal conditioning stimuli were imposed upon the signal for the previously acquired shuttle

avoidance response. Comparison with saline controls showed that chlordiazepoxide did not disrupt fear conditioning. It is also suggested that the decrement produced by chlordiazepoxide was not due to a sensory or motor impairment. 15 references. (Author abstract modified)

065452 Garg, Mithlesh. K.L.D.A.V. College, Meerut University, Roorkee, India Combined effect of drug and drive on the consolidation process. ***Psychopharmacologia (Berlin).*** **18(2):172-179, 1970.**

The combined effect of drug and drive on the consolidation process was studied with rats of the Maudsley strain as subjects. The rats were trained in the Hebb-William's maze under 3 levels of food deprivation, 22, 25, and 7 h (drives) for 10 consecutive days. Immediately after each daily trial the experimental animals of all 3 drives were injected with a 1.0mg/kg dose of picrotoxin, and the animals of the control groups were administered distilled water. Picrotoxin increased the effeciency of learning at all levels of drive, and higher drive level resulted in greater performance. The reactive strain performed better in the maze learning than the nonreactive. 14 references. (Author abstract modified)

065493 Davidson, Arnold B.; Cook, Leonard. Smith Kline & French Laboratories, 1500 Spring Garden Street, Philadelphia, Pennsylvania 19101 Yeast ribonucleic acid: analysis of effects on pole-climb avoidance behavior. ***Psychopharmacologia (Berlin).*** **16(5):399-408, 1970.**

Yeast ribonucleic acid (RNA) treatment increases rate of acquisition of pole - climb avoidance behavior in rats and prolongs retention of this behavior under extinction conditions. These effects of yeast RNA treatment appear to be primarily related to its interaction with components of the behavior which are present even before the emission of the first pole - climb response. Differences were also found between yeast RNA treated rats and control rats in the relationship of performance during acquisition to performance under extinction conditions. These differences suggest that, in addition to its effects before the emission of the first pole - climb response, yeast RNA also interacts with behavior throughout the conditioning procedure. 9 references. (Author abstract)

065747 Glick, Stnaley D.; Jarvik, Murray E. Department of Pharmacology, Albert Einstein College of Medicine, Yeshiva University, 1300 Morris Park Avenue, Bronx, N. Y. 10461 Differential effects of amphetamine and scopolamine on matching performance of monkeys with lateral frontal lesions. ***Journal of Comparative and Physiological Psychology.*** **73(2):307-313, 1970.**

D-amphetamine and scopolamine were administered to 4 monkeys with dorsolateral frontal lesions and 4 unoperated monkeys performing a delayed matching task. Although initially impaired following surgery, the performance of the frontal monkeys on the delayed matching test had recovered to preoperative levels by the time of drug administration. Both d-amphetamine and scopolamine impaired the delayed and nondelayed matching performance of the unoperated control monkeys. However, only scopolamine and not amphetamine impaired the matching performance of the frontal monkeys. The higher doses of both drugs initially decreased the tendencies of both the frontal and unoperated monkeys to respond to the test stimuli. It is proposed that frontal monkeys, unlike normal monkeys, learn to depend upon a nonadrenergic system to solve the matching task and therefore are resistant to certain actions of amphetamine. 25 references. (Journal abstract modified)

065876 Calhoun, William H.; Smith, Allan A.; Bauer, Robert. University of Tennessee, Knoxville, Tennessee 37916 Scopolamine's effect on passive avoidance. ***Psychonomic Sciences.*** **21(3):165-166, 1970.**

Comparison in performance on active and passive retention tests was made for mice that had received scopolamine prior to a single passive avoidance training trial. Control animals performed well with either retention test procedure, while the scopolamine group performed well for the active test but poorly for the passive test. 8 references. (Author abstract)

065933 Reinis, Stanislav. Department of Psychology, York University, 4700 Keele Street, Downsview, Toronto, Ontario, Canada Effect of hydroxylamine on maze learning in mice. ***Journal of Comparative and Physiological Psychology.*** **72(3):512-518, 1970.**

The effect of hydroxylamine on maze learning in mice was studied. An intracranial injection of .5M hydroxylamine given 24 hr. prior to or 1 or 4 hr. following the learning of a water maze impaired animals' retention of the preference for

one arm. An injection 24 hr. after the training session was less effective. The impairment was better expressed if the animals were tested 48 hr. following the training session than if they were tested 24 hr. after training. Exhaustion of animals due to swimming, hypoxia due to methemoglobin formation, and occult seizures did not contribute substantially to the effect. The .3M sodium nitrite in the dose administered intracerebrally also affected the learning and retention of preference to one arm of the water maze. The general trend of the effect of the 2 substances is very similar. 22 references. (Journal abstract modified)

066813 Gardner, Frank T.; Applewhite, Philip B. Biology Department, Yale University, New Haven, Connecticut 06520 Protein and RNA inhibitors and protozoan habituation. ***Psychopharmacologia (Berlin).*** **16(5):430-433, 1970.**

A variety of protein and ribonucleic acid (RNA) inhibitors were tested on habituation learning in the protozoan Spirostomum. Inhibition of protein synthesis up to values of 95% had no effect upon habituation, and RNA inhibition up to 89% by 5-fluorouracil had only slight effects upon it. Large amounts of protein and RNA synthesis are not necessary for habituation. 3 references. (Author abstract)

066821 Cole, Sherwood O. Department of Psychology, Rutgers University, College of South Jersey, Camden, New Jersey 08102 On the combined effects of amphetamine and food deprivation: a reply to Gollub and Mann. ***Psychopharmacologia (Berlin).*** **16(5):426-429, 1970.**

A previously reported interaction of amphetamine and food deprivation on food consumption recently has been called spurious in a report by Gollub and Mann, on the basis of a 'floor' effect interpretation of the data, i.e.,a complete cessation of eating with the larger doses. In reply to this report, a further consideration of the original data indicates 1) such a 'floor' effect does not describe accurately the action of the larger doses, and 2) even the action of the dose that comes closest to satisfying this condition does not in itself explain satisfactorily the interaction. However, analysis of the original data in terms of one additional derived measure of feeding did not yield a statistically significant interaction between amphetamine and food deprivation. The importance of a choice of feeding measure as well as techniques of drug administration and deprivation to such an interaction were briefly considered. 3 references. (Author abstract modified)

066825 Segal, David S.; Whalen, Richard E. Department of Psychobiology, University of California, Irvine, California 92664 Effect of chronic administration of p-chlorophenylalanine on sexual receptivity of the female rat. ***Psychopharmacologia (Berlin).*** **16(5):434-438, 1970.**

It has been postulated that in the female rat sexual receptivity is inhibited by serotonin. This hypothesis was examined by comparing the effects of estrogen and progesterone with the effects of estrogen plus p-chlorophenylalanine (p-CPA), a depletor of brain serotonin, on the induction of sexual receptivity. Progesterone was found to facilitate the effects of estrogen on the induction of receptivity. p-CPA which induced low levels of brain serotonin did not facilitate estrogen induced receptivity. It was concluded that no direct relationship exists between brain serotonin and receptivity. 8 references. (Author abstract)

066828 Fuller, John L. The Jackson Laboratory, Box 258, Bar Harbor, Maine 04609 Strain differences in the effects of chlorpromazine and chlordiazepoxide upon active and passive avoidance in mice. ***Psychopharmacologia (Berlin).*** **16(4):261-271, 1970.**

Strain differences have been demonstrated in the effects of chlorpromazine and chlordiazepoxide upon active and passive avoidance in mice. Four inbred strains of mice were compared on an active and a passive avoidance task in a 2 compartment cage. Active mice were trained to cross frequently between compartments to avoid shock; passive mice were shocked for crossing. Yoked controls in both procedures received shocks at the same time as experimentals. Strains learning the active task well did poorly in the passive task; strains poor in active learning were superior on the passive task. The results support the view that strain differences in avoidance learning are more related to variations in strength of a kinetic drive than to strength of fear. Chlordiazepoxide affected crossings similarly in actively and passively trained Ss; chlorpromazine reduced crossings in actively trained and increased crossings in passively trained Ss. This result is consistent with dual motivational systems differentially susceptible to alternation by administration of drugs. Chlordiazepoxide acts primarily upon kinetic

drive; chlorpromazine upon fear. 8 references. (Author abstract modified)

066829 Scobie, Stanley R.; Garske, George. Department of Psychology, Princeton University, Green Hall, Princeton, New Jersey 08540 Chlordiazepoxide and conditioned suppression. *Psychopharmacologia (Berlin).* 16(4):272-280, 1970.

Chlordiazepoxide (12mg/kg) reduced the suppressive effects of a conditioned emotional response (CER) if the drug was given prior to conditioning stimulus (CS) - shock pairings. No attenuation of suppression occurred if the drug was given prior to the test for suppressive effects of the CS. This attenuating effect of chlordiazepoxide upon CER learning occurred if the behavior suppressed by the CS was either milk licking or lever pressing for food. The effect was dose related with higher dosages causing a greater attenuation of CER learning. 7 references. (Author abstract)

066830 Geller, Anne; Robustelli, Francesco; Jarvik, Murray E. Department of Pharmacology, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, New York 10461 A parallel study of the amnesic effects of cycloheximide and ECS under different strengths of conditioning. *Psychopharamacologia (Berlin).* 16(4):281-289, 1970.

A parallel study is made of the amnesic effects of cycloheximide and electroconvulsive shock (ECS) under different strengths of conditioning of mice. In the experiment, delay of punishment 0, 30, 60, 120 and 240 sec after the step through response in a 1 trial passive avoidance task was used to obtain in mice conditioned responses of different strengths. Both cycloheximide and ECS given immediately after training had a greater amnesic effect upon the weaker conditioned responses obtained with the longer delays of punishment. A proactive effect of ECS, but not of cycloheximide, was demonstrated with the weaker conditioned responses. 18 references (Author abstract modified)

066831 Ayres, John J.B.; Isgrig, Frederick A. Department of Psychology, University of Massachusetts, Middlesex House, Amherst, Massachusetts 01003 Comparisons of 1,3-butanediol and glycerol on several behavioral measures. *Psychopharmacologia (Berlin).* 16(4):290-304, 1970.

Experiments employing rats as Ss were performed to determine the behavioral effects of a prototypic synthetic nutrient, 1,3-butanediol (BD), and to compare these effects with those of glycerol. The following results were obtained: 1) when administered intragastrically to semideprived and nondeprived rats, moderate levels of both BD and glycerol depressed voluntary running activity more than did isocaloric and isovolumetric control substances; 2) for both compounds this depression increased monotonically with increasing dose level, but the effects of BD became relatively more profound than those of glycerol as dose size increased; 3) both compounds monotonically depressed food intake as a function of dose level in tests conducted 3 hr after intubation; 4) the depression of food intake also occurred in restrained Ss, thus was not simply an artifact of depressed activity; 5) increasing doses of BD monotonically depressed water intake for a 3 hr period following intubation, but Ss under Bd could be induced to drink extensively by administering hypertonic salt solutions; 6) increasing glycerol loads had no effect on water intake when running was permitted but increased water intake when running was not permitted; 7) at the highest dose level tested BD profoundly disrupted equilibrium, but glycerol had no effect. These findings suggest that BD may act as a central nervous system (CNS) depressant or muscle relaxant but that glycerol most probably is neither. 7 references. (Author abstract)

066871 Weinreich, D.; Clark, L. D. Department of Pharmacology, University of Utah, College of Medicine, Salt Lake City, Utah 84112 Anticonvulsant drugs and self-stimulation rates in rats. *Archives Internationales de Pharmacodynamie et de Therapie (Gand).* 185(2):269-273, 1970.

The effect of anticonvulsant drugs on the intracranial self-stimulation (ICSS) rates in male Sprague-Dawley rats (12) with electrodes implanted in the median forebrain bundle was studied using diphenylhydantoin, acetazolamide, meprobamate, chlordiazepoxide, phenobarbital, pentobarbital, and pentylenetetrazol. The results indicated that the bartiturates and minor tranquilizers increased ICSS rates, while diphenylhydantoin, acetazolamide, and pentylenetetrazol decreased ICSS rates. The results obtained when using diphenylhydantoin and acetazolamide do not support postulations of previous investigators that drugs that diminish seizure-like behavior poten-

tiate ICSS rates. The results with diphenylhydantoin, acetazolamide, and pentobarbital suggest that drugs may affect ICSS rates without increasing or decreasing seizure activity. 11 references.

05 TOXICOLOGY AND SIDE EFFECTS

066189 Dam, Mogens. Institute of Neurophysiology, Juliane Maries Vej 36, 2100 Copenhagen, Denmark The number of Purkinje cells after diphenylhydantoin intoxication in monkeys. *Epilepsia.* 11(2):199-205, 1970.

The number of Purkinje cells was determined in 2 monkeys intoxicated for 43 and 30 days with 386 and 175 mg/kg of diphenylhydantoin by mouth. The serum levels averaged 90 and 55 mg/l. Symptoms and signs of intoxication appeared at serum concentrations above 20 mg/l and disappeared 7 days after withdrawal of the drug. In brains fixed by perfusion the number of Purkinje cells was the same in the 2 monkeys intoxicated with diphenylhydantoin and in 3 controls. The cerebellar changes in animals reported previously may have been due to fixation artifacts. 14 references. (author abstract)

066935 Spencer, P. S. J.; Waite, R. Department of Pharmacy, University of Aston, Birmingham 4, England Barbiturate-induced sleep in hyperthyroid mice. *European Journal of Pharmacology (Amsterdam).* 11(3):392-394, 1970.

To test the differential hypnotic and acute toxic effects of various barbiturates on hyperthyroid and normal mice, the conditions under which thiopentone is less active in hyperthyroid animals were investigated in male albino mice (18 to 20g). The hyperthyroid animals were injected daily subcutaneously for 10 days with 2mg/kg L-thyroxine sodium, and the euthyroid controls with 0.2ml/20g alkaline normal saline. On day 11, the hypnotic activity and acute toxicity was determined on groups of 15 and 10 animals respectively, by injecting varying doses of pentobarbitone and thiopentone intravenously. In the hyperthyroid mice, there was a significant increase in the duration of sleep following all doses of pentobarbitone, and a significant increase in the acute toxicity. Although thyroxine treatment produced a significant increase in the acute toxicity of thiopentone and prolonged sleep following the highest dose, (50mg/kg), the duration of sleep after the 2 lower doses of thiopentone (30mg/kg and 40mg/kg) was significantly shorter in hyperthyroid mice. Since cerebral blood flow is increased in hyperthyroidism, thiopentone may be redistributed more quickly and have a shorter hypnotic action in hyperthyroid animals. 9 references.

06 METHODS DEVELOPMENT

066415 Nose, Takashi; Kojima, Michio. Department of Pharmacology, Research and Development Division, Tanabe Seiyaku Company, Osaka, Japan A simple screening method for antiparkinsonian drugs in mice. *European Journal of Pharmacology (Amsterdam).* 10(1):83-86, 1970.

A number of antiparkinsonian and miscellaneous drugs were examined for their ability to protect mice from physostigmine-induced death and tremorine, oxotremorine and nicotine induced tremors. Typical antiparkinsonian drugs, such as centrally acting anticholinergics (hyoscine, atropine, benztropine, trihexyphenidyl, procyclidine, biperiden and ethopropazine) and antihistamines (promethazine and diphenhydramine) were effective against physostigmine-induced death, whereas other drugs, ineffective in parkinsonian therapy, were ineffective. The use of the physostigmine-induced death method in preliminary screening for antiparkinsonian drugs in mice was more specific than either the tremorine or oxotremorine tremor method. 10 references. (author abstract)

066738 Forrest, I. S.; Rose, S. D.; Brookes, L. G.; Halpern, B.; Bacon, V. A.; Silberg, I. A. Biochemical Research Laboratory, MPD, Veterans Administration Hospital, Palo Alto, California 94304 Fluorescent labeling of psychoactive drugs. *Agressologie (Paris).* 11(2):127-133, 1970.

Fluorescent derivatives of demethylated or hydroxylated metabolites of the psychoactive drugs chlorpromazine, imipramine and amitriptyline have been prepared by 'dansylation' (reaction with 1-dimethylaminophthalene-5-sulfonyl chloride). These compounds have been characterized by thin layer chromatography, spectrophotofluorometry and mass spectrometry. They will serve as reference compounds for identification and assay of biotransformation products of these drugs in biological material from patients and experimental animals. 6 references. (Author abstract)

ABSTRACTS

CLINICAL PSYCOPHARMACOLOGY

07 EARLY CLINICAL DRUG TRIALS

064639 Turek, I. S.; Ota, K.; Machado, R.; Ferro-Diaz, P.; Kurland, A. A. Spring Grove State Hospital, Maryland Psychiatric Research Center, Catonsville, Maryland The use of SU 17595 A in the treatment of psychiatric disorders. ***Current Therapeutic Research.*** **12(8):532-535, 1970.**

The effectiveness, tolerance and therapeutic dosage of SU-17595A was studied on 33 newly admitted, chronic mental patients with a wide range of psychiatric symptomatology. Following a 5 day drug free assessment period, SU-17595A was administered in a dosage range of 75 to 300mg per day for 6 weeks. The symptomatic improvement was measured on the Brief Psychiatric Rating Scale weekly. Two of 3 alcoholics improved moderately; 1 neurotic depressive improved slightly and 2 worsened; 1 psychotic depressive improved slightly; 4 of 6 paranoid schizophrenics showed slight improvement; 6 of 11 chronic undifferentiated schizophrenics showed slight dimunition of suspiciousness and agitation, and 4 of these had less hallucinations and bizarre behavior; and 9 patients dropped out of the study. The effect of SU-17595A in the control of psychotic symptomatology was considerably less than that demonstrated by the commonly used phenothiazines; it is therefore not a drug of choice in the treatment of severe symptoms of psychosis. There was no evidence of harmful effects. 2 references.

065458 Kline, N. S.; Simpson, G. M.; Swenson, J. E. Research Center, Rockland State Hospital, East Orangeburg, New York Private ambulatory patients treated with fluphenazine enanthate. ***Diseases of the Nervous System.*** **Supplement:31(9):43-45, 1970.**

Treatment of private ambulatory patients with fluphenazine enanthate is reported. Despite the high incidence of extrapyramidal side-effects, long acting parenteral fluphenazine enanthate is a unique therapeutic agent. Results of treatment with 44 ambulatory schizophrenics and manics are presented. A relationship between size of dose and response is demonstrated. Without this drug a substantial number of patients to whom it was given would otherwise have required hospitalization. (Author abstract modified)

065473 Kurland, Albert A.; Dim, Bomen H.; Olsson, James E. Maryland Psychiatric Research Center, Baltimore, Maryland The effectiveness of parenteral administration of fluphenazine decanoate in the treatment of chronic schizophrenics. ***Diseases of the Nervous System.*** **Supplement 31(9):18-23, 1970.**

The results of the present study were taken as demonstrating the effectiveness of parenteral administration of fluphenazine decanoate as a maintenance treatment for chronic schizophrenic patients previously found to be responsive to oral fluphenazine. Thirteen patients completed the decanoate treatment course, which averaged 6 months in length. Three patients were discontinued because of poor therapeutic response. Psychiatrists' ratings of discomfort and adaptability revealed no significant differences between oral fluphenazine and decanoate treatment. Data concerning the number of decanoate injections, length of intervals between injections, and dosage levels were also reported. The advantages and disadvantages of fluphenazine decanoate treatment were discussed in terms of ease and reliability of administration, extrapyramidal effects, and blood pressure changes. (Author abstract)

065474 Neal, C. D.; Imlah, N. W. Shelton Hospital, Shrewsbury, Shropshire, England Institutional management of chronic schizophrenics with fluphenazine decanoate. ***Diseases of the Nervous System.*** **Supplement 31(9):24-27, 1970.**

On the basis of the results reported, it would appear that fluphenazine decanoate has a place in the treatment of hospitalized chronic schizophrenic patients. The initial injection of 12.5mg produced a rapid response with the maximal effect appearing within the first 7 days. This observation is supported by a reduction in the score of the brief psychiatric rating scale of 30% over this period. By the third and fourth day of the trial, the nurses behavior rating scale also fell by approximately 25%. It is impossible to estimate accurately the duration of effect from a single injection of 25mg over a period of 5 weeks. However, the mean duration of effect appears to fall between 3 and 4 weeks. In general, the drug was well tolerated. All 20 patients showed signs of extrapyramidal reactions; however, in the great majority of cases they were mild. (Author abstract modified)

066465 No author. Author address not given Drug combination allows smaller doses of L-dopa. *Geriatrics.* 25(8):64, 1970.

Combined treatment with L-dopa and alpha-methyldopa hydrazine (MK485) in depressed patients may increase the number of patients able to tolerate doses of L-dopa sufficient to affect the central nervous system and possibly may shorten the time required to attain an optimal therapeutic dose. MK485 appears to be an effective peripheral inhibitor of dopa decarboxylase. A nonrandom, double -blind study was done on 9 hospitalized, depressed patients treated with MK485 (750 to 1,000mg daily) and L-dopa (300 to 1,500mg daily) in alternating drug and placebo periods. Three patients improved on the combination treatment, 6 showed no change, but 2 of the 3 who had improved, relapsed during the placebo period. Similar plasma dopa levels were noted in patients receiving L-dopa and MK485 combination and patients receiving L-dopa alone at 10 times the dosage. Using the combination of drugs facilitates the administration of L-dopa in patients heretofore unable to tolerate high doses of L-dopa alone, due to peripheral side-effects.

066748 Young, Edwin. Wolston Park Hospital, Wacol, Queensland 4076, Australia Hospital experience with fluphenazine enanthate. *Diseases of the Nervous System.* 31(10):705-709, 1970.

Hospital experience with fluphenazine enanthate in treatment of chronic schizophrenia and mental retardation is reported. Results of the drug trial are: 1) in chronic schizophrenics, 51% showed improvement in overall behavior above their previous treatment level when treated with fluphenazine enanthate; 2) in mentally retarded patients permanently institutionalized, 22% showed improvement in behavior on fluphenazine enanthate over their previous treatment level; 3) approximately 30% of all patients experienced extrapyramidal reactions which were readily controlled by benzhexol and did not appear to be related to age or dosage; side effects from previous phenothiazine treatment (weight gain, skin changes) disappeared; 4) the advantages of convenience of administration, certainly of effective dosage, saving of time and overall economy were appreciated by hospital administration, staff and patients. 15 references. (Author abstract modified)

066826 McLeod, William R.; Mowbray, Robert M.; Davies, Brian. University Department of Psychiatry, Royal Melbourne Hospital, Melbourne, Victoria, Australia Trials of Ro 5-3350 and diazepam for anxiety symptoms. *Clinical Pharmacology and Therapeutics.* 11(6):856-861, 1970.

Clinical trials of diazepoxide compound, Ro 5-3350, and diazepam were made to assess the value of these drugs in treatment of anxiety symptoms. Problems of assessment of antianxiety drugs are discussed and the use of small scale controlled preliminary clinical trials is suggested. Two such trials are described. In each the effects of the active substance were compared with placebo in persistently anxious patients with the use of a partially balanced design. In the first trial no differences were found between Ro 5-3350 at 5 and 10mg. 3 times a day and placebo. In the second trial conducted with similar patients and for the same length of time, different ratings of change were used, and diazepam was found to be superior to placebo. 6 references. (Author abstract modified)

08 DRUG TRIALS IN SCHIZOPHRENIA

064638 Yaryura-Tobias, Jose A.; Diamond, Bruce; Merlis, Sidney. Research Division, Central Islip State Hospital, Central Islip, New York The action of L-dopa on schizophrenic patients (a preliminary report). *Current Therapeutic Research.* 12(8):528-531, 1970.

The action of L-dopa on schizophrenic patients was studied in 5 male chronic schizophrenic patients, 2 paranoid and 3 undifferentiated. Dosage was increased from 200mg to 1g daily during the first 9 days, and by 200 mg increments for the next 5 days to 2g daily. Patients were maintained on 2g daily for 1 week, then switched to placebo for 1 week. Four patients were receiving concurrent neuroleptic medication. L-dopa increased alertness in patients with initial symptoms of withdrawal and poor communication, and worsened the baseline paranoid symptoms in 2 patients. Increased sexual urges occurred in 2 patients and auditory hallucinations in 4. In all patients, all changes appeared at the 1g dose level and worsened as the 2g dosage was approached. Since psychiatric symptoms have been observed in parkinsonian patients treated with L-dopa, excess of dopamine may cause or aggravate mental symptoms. Psychiatric symptoms caused by L-dopa administration may not only be a side-effect, but may be considered a probable precursor in some mental diseases. 12 references.

065416 Hawkins, David R.; Bortin, Aaron W.; Runyon, Richard P. North Nassau Mental Health Center, Manhasset, New York Orthomolecular psychiatry: niacin and megavitamin therapy. *Psychosomatics.* 11(5):517-521, 1970.

A brief outline of the concept of orthomolecular psychiatry and its clinical application to schizophrenia has been described. This approach utilizes an overall biochemical as well as pharmacologic approach in an attempt to correct either demonstrated or hypothesized biochemical abnormalities. An aftercare study including 160 patients in whom half were continued on megavitamin therapy is described and a correlation was established showing that the relapse rate amongst the megavitamin therapy group was approximately one-half that of the control group. These findings suggest that further investigations of this therapeutic approach are warranted since orthomolecular therapy may be found to be of great value and may turn out to be the best method of treatment for many patients. 112 references. (Author abstract)

065475 Bucci, Luigi; Fuchs, Maria; Simeon, Jovan; Fink, Max. Division of Psychopharmacology, Department of Psychiatry, New York Medical College-Metropolitan Mental Health Center, New York, New York Depot fluphenazine in the treatment of psychosis in a community mental health clinic. *Diseases of the Nervous System.* Supplement 31(9):28-31, 1970.

Consecutive schizophrenic patients in a community mental health clinic were given either depot fluphenazine decanoate or depot fluphenazine enanthate. After stabilization, 40 patients were transferred to the other dosage form. Both drugs successfully modified the psychotic pattern in 87.5% of the cases. The average dose and interinjection intervals were 0.88 and 0.91cc and 18.9to 20.6days. Priming with oral fluphenazine was not necessary to achieve satisfactory clinical effects with either depot form. (Author abstract)

065476 Itil, T.; Keskiner, A. Department of Psychiatry, University of Missouri, St. Louis, Missouri Fluphenazine hydrochloride, enanthate, and decanoate in the management of chronic psychosis. *Diseases of the Nervous System.* Supplement 31(9):37-42, 1970.

A summary of the results of clinical comparisons of fluphenazine hydrochloride, fluphenazine eneathate, and fluphenazine decanoate in the management of chronic psychosis is presented. The studies included treatment of chronic schizophrenics, hospitalized schizophrenics, and schizophrenic outpatients. Long acting fluphenazine decanoate and enanthate were found to be very effective as a substitute for daily oral psychotropic drugs in nonhospitalized schizophrenics. Enanthate seemed to have a shorter duration of effectiveness with more extrapyramidal side reactions than decanoate. (Author abstract modified)

065477 Goldberg, Harold L.; DiMascio, Alberto; Chaudhary, Basudeo. Boston State Hospital, Boston, Massachusetts A clinical evaluation of fluphenazine enanthate. *Diseases of the Nervous System.* Supplement 31(9):46-47, 1970.

A clinical evaluation of fluphenazine enanthate has been made in 45 patients with a primary diagnosis of schizophrenia. Seventeen of these patients were inpatients and the other 28 were to receive home treatment. The results indicate that prolixin enanthate appears to be significantly superior to orally administered phenothiazine in drug reluctant patients. It was most outstanding in paranoid individuals. It was remarkably useful in patients seen at home who refused medication, many of whom would have required hospitalization had this drug not been available. The drug was easily administered intramuscularly in the deltoid region by a nurse making home visits and was well tolerated by all of the patients treated at home. (Author abstract modified)

065478 Polvan, N. Noropsikiyatri Klinigi, Cerrahpasa, Istanbul, Turkey Fluphenazine hydrochloride and enanthate in the management of chronic psychosis. *Diseases of the Nervous System.* Supplement 31(9):48-49, 1970.

Clinical studies of fluphenazine hydrochloride and fluphenazine enanthate in the management of chronic psychosis are reported. Effects of dif ferent dosages were compared in treatment of schizophrenics in Instanbul (hydrochloride) and in the United States (enanthate). According to the results from fluphenazine hydrochloride treatment, the drug is more effective and causes fewer side-effects if a high dosage is given (100mg as initial dose, and increasing it every second day 100mg to 600-800mg) than if a lower dosage is given (25 to 60mg) to chronic therapy resistant schizophrenic patients. It was found that fluphenazine enanthate is an effective, long acting

psychotropic drug which can be used in ambulatory cases with acute symptomatology. Side-effects are described. (Author abstract modified)

065479 Wintrob, Ronald M. Department of Psychiatry, University Connecticut Health Center, McCook Hospital, 2 Holcomb Street, Hartford, Connecticut Long acting phenothiazines and long term psychotic patients: the role of fluphenazine enanthate in treatment. *Diseases of the Nervous System.* Supplement 31(9):50-62, 1970.

The role of fluphenazine enanthate in treatment of long-term psychotic patients has been evaluated in an attempt to find a long acting tranquilizing drug effective in ongoing management of these patients. Fluphenazine enanthate was administered in 25mg. intramuscular biweekly injections to 14 Liberian patients with a history of severe and recurrent psychotic reactions over the course of several years, and whose cooperation in ongoing maintenance therapy was notably limited. Ten of the 14 schizophrenic patients responded favorably to the drug. The onset of action was variable, with a range of 3 days to 2 weeks being most representative. An asymptomatic fall in blood pressure of 5-15 mm. Hg. was also characteristic. Extrapyramidal reactions were frequent, occurring in 9 of the 14 patients studied, but could be adequately managed with oral anticholinergic drugs and did not represent an impediment to the continued use of fluphenazine enanthate. Fluphenazine enanthate appears to be useful and effective in the long-range management of patients with long-term psychotic illness and limited level of cooperation in ongoing therapy. (Author abstract modified)

066398 Gonier, Thomas; Schiele, Burtrum C.; Vestre, Norris D. Veterans Administration Hospital, St. Cloud, Minnesota A comparison of haloperidol and thioridazine HCl in chronic treatment-resistant schizophrenics. *Behavioral Neuropsychiatry.* 2(3-4):47-49, 54, 1970.

A double-blind trial of haloperidol versus thioridazine with 40 hospitalized phenothiazine - refractory, chronic, schizophrenic males was conducted for 12 weeks. Average daily dosages at the endof the treatment period were 9.3mg haloperidol and 734.2mg thioridazine. Despite a clerical error in the random assignment of patients to the two treatment groups, the results suggest that haloperidol was more effective in reducing the more typically psychotic symptoms, e.g.,conceptual disorganization, and that thioridazine was more effective in reducing symptoms of a more neurotic nature, e.g.,guilt feelings and somatic concern. Although analysis of side-effects data revealed no statistically significant differences between treatments, more side-effects appeared to occur with haloperidol, and five patients in the haloperidol group required antiparkinson medication as compared to one patient in the thioridazine group. 8 references. (author abstract)

066817 Gonier, Thomas; Schiele, Burtrum C.; Vestre, Norris D. Veterans Administration Hospital, St. Cloud, Minnesota A comparison of haloperidol and thioridazine HCl in chronic treatment-resistant schizophrenics. *Physicians' Drug Manual.* 1(12):256-259, 1970.

A comparison is made of haloperidol and thioridazine hydrochloride in chronic treatment resistant schizophrenics. A double-blind trialof haloperidol versus thioridazine with 40 hospitalized phenothiazine -refractory schizophrenic males was conducted for 12 weeks. Average daily dosages at the end of the treatment period were 9.3mg haloperidol and 734.2mg thioridazine. Despite a clerical error in the random assignment of patients to the 2 treatment groups, the results suggest that haloperidol was more effective in reducing the more typically psychotic symptoms, e.g.,conceptual disorganization, and that thioridazine was more effective in reducing symptoms of a more neurotic nature, e.g.,guilt feelings and somatic concern. Although analysis of side-effects data revealed no statistically significant differences between treatments, more side effects appeared to occur with haloperidol, and 5 patients in the haloperidol group required antiparkinson medication as compared to 1 patient in the thioridazine group. 8 references. (Author abstract modified)

066852 Krumholz, W. V.; White, L. Clinical Facilities and Research Division, Central Islip State Hospital, Central Islip, New York Clinical evaluation of Mazindol in chronic schizophrenics. *Current Therapeutic Research.* 12(9):609-610, 1970.

The effects of Mazindol (3, 6, 9, 12 and 9mg daily during the first, second, third, fourth, fifth and sixth weeks of medication respectively) on 12 chronic schizophrenic female patients were evaluated using the Brief Psychiatric Rating Scale (BPRS), the Nurses' Observation Scale for Inpatient Evaluation (NOSIE) and the Clinical Global

Impressions (CGI) forms. Patients became increasingly worse during the course of the study. Ratings on the BPRS reflected increased emotional withdrawal, mannerisms, uncooperativeness and disorientation. On the NOSIE, social competence, personal neatness, manifest psychosis and total patient assets improved. Side-effects included dose related increases in supine and standing radial pulse and general increases in supine diastolic blood pressure. Drowiness, excitement, depression and tachycardia were other frequently cited symptoms. Thus, Mazindol is not indicated in chronic schizophrenia. 1 reference.

09 DRUG TRIALS IN AFFECTIVE DISORDERS

064637 Solis, Hernan G.; Molina, Gilberto B.; Pineyro, Alfredo. Psychiatric Unit, School of Medicine, University of Nuevo Leon, Mexico Clinical evaluation of doxepin and amitriptyline in depressed patients. *Current Therapeutic Research.* 12(8):524-527, 1970.

A comparative evaluation of doxepin and amitriptyline was made in a double-blind study on 11 male and 23 female patients presenting all types of depression. During an 8 week treatment period, 21 patients received doxepin and 13 received amitriptyline. With doxepin, the total daily dose was 75mg for 16 patients and 100 to 150mg for 5 patients; with amitriptyline, the total daily dose was 75mg for 10 patients and 100 to 150mg for 3 patients. Evaluation of response to the 2 drugs was done with Zung's Self-Rating Depression Scale. The therapeutic effect of doxepin began in the first week, while the effect of amitriptyline began in the third week of treatment. Doxepin showed a greater antidepressive effect than amitriptyline, was effective in the treatment of schizophrenic depressive patients, and had an anxiolytic effect in cases of depressive neurosis, involutional psychosis, and schizophrenia with depression. Side-effects included somnolence, dizziness and dryness of mouth and resulted in discontinuance of drug administration in 1 case each for doxepin and amitriptyline. 8 references.

065165 Bunney, William E., Jr. Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Md. Present status of psychological reactions to L-DOPA. *American Journal of Psychiatry.* 127(3):361-362, 1970.

The use of L-Dopa in depressed and parkinsonian patients is discussed briefly and the need for colloboration between neurologists and psychiatrists is pointed out. Administered in large doses it has been a great help in parkinsonism, although it has psychological side effects, most of which aretemporary and most of which relate to preexisting pathology. Administered in large doses to depressed patients it has produced some improvement, although there are side effects, as there are with schizophrenic subjects. With peripheral decarboxylase inhibitors, L-Dopa can be given in smaller amounts and may prove more beneficial and may show fewer side effects. 7 references.

065480 Lambert, P. A.,; Marcou, G. Hospital de Bassens, Chambery, France Fluphenazine enanthate given to inpatients and outpatients. *Diseases of the Nervous System.* Supplement 31(9):63-65, 1970.

Clinical experience in therapeutic use of fluphenazine enanthate for psychotic inpatients and outpatients is reported after 27 months of use of the drug. Fluphenazine enanthate was administered to 110 patients. The treatment lasted more than 2 years for some patients. The average length of treatment was 13 months. Fifty seven of the patients were outpatients and 53 were inpatients. By comparing both inpatients and outpatients it appears that: 1) outpatients need less fluphenazine enanthate than inpatients; 2) time between injections is longer for outpatients than for inpatients; and 3) injections are well tolerated without biological changes. The most frequent side-effects are asthenia, depression, and chronic dyskinesia. Fluphenazine enanthate is particularly adapted to long-term treatment. It increases the patient's cooperation by impressing on him the need for frequent medical checkups which can be done when he is getting his injections. Fluphenazine enanthate reduces potential toxicity by reducing the amount of major tranquilizer given. It is useful for most chronic psychotic patients, particularly rehabilitated schizophrenics. (Author abstract modified)

065691 Kane, Francis J., Jr. North Carolina Memorial Hospital, Chapel Hill, North Carolina 27514 Carbon disulfide intoxication from overdosage of disulfiram. *American Journal of Psychiatry.* 127(5):690-694, 1970.

A case is discussed of acute brain syndrome with depression, peripheral neuropathy, and transient parkinsonism following ingestion of large amounts of disulfiram. Clinical and experimental evidence bearing on the relationship between disulfiram and its metabolite, carbon disulfide, and similarities in the syndromes associated with the toxicity of each, are reviewed. 20 references. (Journal abstract modified)

065851 Laurell, Bjorn. University of Umea, Umea, Sweden Comparison of electric and flurothyl convulsive therapy. II. antidepressive effect. *Acta Psychiatrica Scandinavica*. Supplement 213:22-35 (1970).

Flurothyl (Indoklon) convulsive therapy (ICT) and electroconvulsive therapy (ECT) were compared with regard to therapeutic efficiency in endogenous depression. The design was double-blind and the comparison was made between 2 random groups comprising 29 (ECT) and 30 (ICT) patients with endogenous depression. Generalized seizures were elicited by inhalation technique in ICT and by bilaterial stimulation in ECT. Treatment technique was standardized and the number of treatments was free. The patients were rated with Cronholm-Ottosson's depression rating scale before the first treatment, 4 days and 1 month after the end of the treatment series. The patient groups were fairly similar in respect to several background variables and initial rating scores. The results were similar in the 2 groups with regard to the following measures related to therapeutic efficiency: 1) the depression rating scores at the end of the treatment and difference between initial and final scores; 2) the global rating scores at the end of the treatment. There was a tendency in favor of ICT. It may be concluded that the therapeutic efficiency in endogenous depression is fairly similar in ECT and ICT. A slight tendency to better results in the ICT group can at least partly be explained by more favorable prognostic factors. 29 references. (Author abstract modified)

066322 Matussek, N.; Benkert, O.; Schneider, K.; Otten, H.; Pohlmeier, H. Max-Planck-Institut fur Psychiatrie, Munich 23, West Germany L-dopa plus decarboxylase inhibitor in depression. *Lancet (London)*. No. 7674:660, 1970.

In a letter to the editor, a trial of L-dopa in combination with a decarboxylase inhibitor in the treatment of patients with retarded depression is reported. The decarboxylase inhibitor tested was N1-(D 2-seryl-N2-(2,3,4-trihydroxybenzyl)-hydrazine) hydrochloride (Ro 4-4602). Of 31 patients, 18 received active treatment, 13 received placebo. The patients received 150mg of Ro 4-4602, with 150mg L-dopa administered after 3 days on Ro 4-4602. The active treatment group showed greater and more significant improvement, and less worsening, than the placebo group. However, most patients in the active treatment group improved only slightly. This may be a result of their having received only small doses of L-dopa. It is suggested that if the L-dopa dose were increased, improvement might be more noteworthy. 3 references.

067013 Hussain, Zulfiquar. Cherry Knowle Hospital, Sunderland, County Durham, England Drugs in depressive illness. *British Medical Journal (London)*. No. 5707:482, 1970.

In a letter to the editor in reply to previous studies in which it was suggested that milder forms of depression can be treated with support and a placebo, preliminary findings from a double-blind trial of antidepressants are presented. Fifty four patients were treated, 15 of whom received amitriptyline and perphenazine, 20 of whom received perphenazine, and 19 of whom received a placebo containing atropine. Each of the patients was randomly allocated to one of the treatments and assessed on 3 occasions in terms of 15 symptoms plus an overall rating. A statistical analysis of the findings showed a chi square of 1.52, implying a lack of significant difference between the treatments. These results tend to support the view that antidepressant drugs are sometimes established in clinical practice on inadequate evidence. 2 references.

10 DRUG TRIALS IN NEUROSES

065235 Lapolla, Anthony; Jones, Harry. Camarillo State Hospital, Camarillo, California 93010 Placebo-control evaluation of desipramine in depression. *American Journal of Psychiatry*. 127(3):335-338, 1970.

A double-blind clinical trial was conducted to compare the effectiveness of desipramine and placebo in newly hospitalized patients. Analysis of data from 74 patients (34 on desipramine, 40 on placebo) showed that in patients with endogenous depression, the response to desipramine was superior to response to placebo as early as the fifth day of treatment; in patients with neurotic (reac-

tive) depression, no significant differences in response were found. 11 references. (Author abstract)

065247 DeSilverio, Robert V.; Rickels, Karl; Weise, Charles C.; Clark, Edward L.; Hutchinson, James. Philadelphia General Hospital, Philadelphia, Pennsylvania Perphenazine-amitriptyline in neurotic depressed outpatients; a controlled collaborative study. ***American Journal of Psychiatry.*** **127(3):322-329, 1970.**

The combination of perphenazine and amitriptyline was compared to each of its constitutents in a double-blind study conducted with 138 depressed and anxious depressed neurotic outpatients. Irrespective of drug, general practice patients improved the most, clinic patients somewhat less, and private psychiatric patients the least. Drug differences were limited to a few significant and borderline significant effects present only at two weeks; they indicated that perphenazine produced the greatest improvement at this period. 14 references. (Author abstract)

065314 Yaryura-Tobias, Jose A.; Diamond, Bruce; Wolpert, Arthur; Merlis, Sidney. Central Islip State Hospital, Central Islip, New York The variables of silent myocardial infarction in a psychotic population. ***Psychosomatics.*** **11(5):483-487, 1970.**

A preliminary investigation of the elements that could be an integral cause of silent myocardial infarction in psychotics is reported. Verbal pain threshold tests appeared to support the hypothesis that one element could be an etiological factor due to difference in pain threshold. Results were essentially negative when testing the analgesic action of phenothiazines as a possible element. It was found that phenothiazine medication tends to restrict and inhibit the infarction subjects' ability to communicate. 6 references.

065446 Hesbacher, Peter T.; Rickels, Karl; Hutchison, James; Raab, Ernst; Sablosky, Lester; Whalen, Edward M.; Phillips, F. J. Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania Setting, patient, and doctor effects on drug response in neurotic patients: II. differential improvement. ***Psychopharmacologia (Berlin).*** **18(2):209-226, 1970.**

Differential effects of treatment setting, patient and doctor on drug response in neurotic patients are investigated. Diazepam was compared to placebo and phenobarbital sodium in a double-blind study with 472 anxious psychoneurotic patients. Patients were treated in 3 settings -- medical clinic, general practice and private psychiatric practice. The treatment setting was found to be at least as important as the medication in producing a treatment response. Compared to placebo, both diazepam and phenobarbital produced more clinical improvement. In general practice the 2 active drugs were about equally effective. In private psychiatric practice the treatment of choice was diazepam. In medical clinic the treatment of choice, particularly after 4 weeks of medication, was phenobarbital. These differences do not appear to be explained by doctor effects. Rather, these differences seem to depend upon patient behavior patterns and social class as well as upon a medical as opposed to a psychiatric orientation to treatment. In determining a given drug treatment, the physician, however, has to consider not only clinical improvement, but also drug related side effects, particularly sedation in this case. And here diazepam has a great advantage over phenobarbital, even in the general practice population. It is concluded that diazepam represents the treatment of choice for both middle social class populations, general practice and private psychiatric practice, while phenobarbital represents the treatment of choice for low social class medical clinic patients. 13 references. (Author abstract modified)

065453 Hesbacher, Peter T.; Rickels, Karl; Gordon, Paul E.; Gray, Bruce; Meckelnburg, Robert; Weise, Charles C.; Vandervort, W. J. Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania 19104 Setting, patient, and doctor effects on drug response in neurotic patients: I. differential attrition, dosage deviation, and side reaction responses to treatment. ***Psychopharmacologia (Berlin).*** **18(2):180-208, 1970.**

The effects of differential attrition, dosage deviation and side reaction response to treatment, comparing diazepam to placebo and phenobarbital sodium, were investigated in a double-blind study with 472 anxious psychoneurotic patients. Setting, patient and doctor effects on drug response were observed in the study. Patients were treated in 3 settings -- medical clinic, general practice, and private psychiatric practice. The treatment setting was found to be at least as important as the medication in producing a treatment response. Drug effects were pronounced. Compared to phenobarbital patients, diazepam patients more often

completed the study, followed prescribed dosage, and reported fewer side reactions. Diazepam patients did not differ from placebo patients in dosage intake or side effects, only in higher completion rate. Population effects indicated clinic patients to drop out and deviate from dosage more than private patients. General practice patients reported the most and private psychiatric patients reported the least side effects. These differences are explained in terms of patient background and behavioral patterns and of a medical as opposed to a psychiatric orientation toward treatment. 42 references. (Author abstract modified)

065488 Rickels, Karl; Lipman, Ronald S.; Fisher, Seymour; Park, Lee C.; Uhlenhuth, Eberhard H. 203 Piersol Building, University Hospital, 3400 Spruce Street, Philadelphia, Pennsylvania 19104 Is a double-blind clinical trial really double-blind: a report of doctors' medication guesses. *Psychopharmacologia (Berlin).* 16(4):329-336, 1970.

In an attempt to determine if a double-blind clinical trial is truly double-blind, a double-blind trial of meprobamate and placebo was carried out with 138 anxious neurotic outpatients. Psychiatrists performed medication guesses after 2, 4, and 6 weeks of therapy. At the same time, physician and patient independently completed several improvement measures and the physician recorded the presence or absence of side reactions as spontaneously reported by the patient. The results may be summarized as follows: a) clinical improvement and side-effects often enable the physician to make reliable medication guesses and thus break the double-blind design in drug trials; b) clinical improvement seems to exert the most important influence in determining physician medication guesses, at least with antianxiety drugs in studies of only 4 to 6 weeks duration; c) the correlation between side-effects and medication guesses increases with the duration of therapy. 7 references. (Author abstract modified)

066276 Rickels, Karl; Clark, Edward L.; Etezady, Mohammad H.; Sachs, Ticu; Sapra, Ravi K.; Yee, Robert. Private Practice Research Group, Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania Butabarbital sodium and chlordiazepoxide in anxious neurotic outpatients: a collaborative controlled study. *Clinical Pharmacology and Therapeutics.* 11(4):538-550, 1970.

Butabarbitual sodium, a barbiturate rather widely used in the symptomatic treatment of anxiety, particularly in nonpsychiatric practice, was compared with chlordiazepoxide, a standard antianxiety agent, and placebo in 138 psychiatric and nonpsychiatric patients suffering from anxiety. Patients were instructed to take a capsule 4 times a day; each capsule contained 30mg butabarbitual sodium or 10mg chlordiazepoxide or an inert substance. Data on the 95 patients who completed the 4 week double-blind study were analyzed with the use of a factorial analysis of covariance design, and the main findings were as follows: (1) Butabarbital sodium and chlordiazepoxide produced significantly more clinical improvement than placebo. (2) General practice patients improved the most, private psychiatric patients somewhat less, and medical and psychiatric clinic patients the least. (3) Both private practice populations improved the most on active drugs and the least on placebo, leading to significant drug - placebo differences only in these 2 populations. Factorial covariance analyses testing for the effect of initial level of anxiety on clinical improvement consistently indicated that, within all 4 populations, 'high' anxious patients responded less well to placebo and better to drug than 'low' anxious patients. Several global improvement measures indicated chlordiazepoxide to be superior to butabarbital sodium irrespective of population, while more circumscribed measures showed butabarbital sodium to be particularly effective in general practice patients, with chlordiazepoxide slightly favored in private psychiatric patients. An explanation of these somewhat conflicting findings is not presently available, and further research on butabarbital sodium is suggested. 7 references. (author abstract modified)

066440 Abrams, Richard. Department of Psychiatry, New York Medical College, New York, New York 10029 L-dopa with MK 485 for depression. *Lancet (London).* 7661:1394, 1970.

Dr. Goodwin's and his colleagues' report of the treatment of depressed patients with L-dopa and a peripheral decarboxylase inhibitor (Lancet, May 2, 1970, p.908) is criticized for its lack of direct psychiatric assessment. It was also felt the authors had poorly defined improvement as a 3 point change on a 15 point scale. No figures were given for the range of scores, their means, standard deviations or change with treatment. It is pointed out that the import of the work that was

reported depends on whether depressed patients improve significantly with L-dopa (with or without MK 485), and that this cannot be ascertained from the information as it was presented.

066496 Schapira, Kurt; McClelland, H. A.; Griffiths, N. R.; Newell, D. J. University of Newcastle upon Tyne, Newcastle upon Tyne, England Study on the effects of tablet colour in the treatment of anxiety states. ***British Medical Journal (London).*** **No. 5707:446-449, 1970.**

The role of tablet color in the drug treatment of patients with anxiety states was studied. The study was designed to permit comparison of patients self rating assessments with those made by the physicians. Forty eight patients with anxiety states were treated with oxazepam (Serenid-D), which was administered in red, yellow and green. Every patient received one week's treatment with each color, according to a random program. A latin square design was used to ensure completebalance between the colors and between the weeks. The patients' symptoms were categorized and then assessed by both weekly physicians' ratings and daily self rating, which showed close agreement. Color preference was shown on both these scales in that symptoms of anxiety were most improved with green, whereas depressive symptoms appeared to respond best to yellow. Such color preferences, however, did not reach levels of statistical significance, except for phobias as rated on the physicians' assessment. The results indicate that color may play a part in the response to a drug. 10 references. (author abstract modified)

066709 Rickels, Karl; Gordon, Paul E.; Gansman, David H.; Weise, Charles C.; Pereira-Ogan, Jorge A.; Hesbacher, Peter T. The Private Practice Research Group, Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania Pemoline and methylphenidate in mildly depressed outpatients. ***Clinical Pharmacology and Therapeutics.*** **11(5):698-710, 1970.**

Pemoline and methylphenidate hydrochloride were compared to placebo in a double-blind study of mildly to moderately depressed outpatients with target symptoms of fatigue, apathy, anorexia. Patients attended either the psychiatric clinic of a large city hospital or the offices of several general practitioners and private psychiatrists. Clinic patients had significantly lower educational and occupational levels than the middle class private practice patients. At 2 and 4 weeks, both pemoline and methylphenidate produced significantly more improvement than placebo in clinic and general practice patients. Private psychiatric patients, however, improved as much or even slightly more on placebo than on either drug. A number of explanations are put forward. 11 references. (Author abstract)

066832 Rickels, K.; Hesbacher, P. T.; Weise, C. C.; Gray, B.; Feldman, H. S. 203 Piersol Building, University Hospital, 3400 Spruce Street, Philadelphia, Pennsylvania 19104 Pills and improvement: a study of placebo response in psychoneurotic outpatients. ***Psychopharmacologia (Berlin).*** **16(4):318-328, 1970.**

The hypothesis that clinical improvement would be significantly correlated with number of daily placebo pills prescribed was supported for clinic and general practice patients but not for private psychiatric practice patients. Patients in the 3 treatment settings differed in other ways, particularly in treatment orientation, i.e.,their awareness of having emotional problems and the most suitable treatment recommended for them by their physicians, as well as in social class. Treatment orientation was found not to account for the demonstrated 'pill effect', and social class differences, seen only in general practice, also did not appear to modify the relationship between pills and improvement within the entire patient sample. Our findings in this study have methodological as well as clinical implications. The fact that higher placebo intake levels resulted in reduced drug placebo differences in improvement poses a practical problem for the clinical researcher, while the lack of placebo improvement observed at lower placebo intake levels indicates that 1 placebo pill per day is not a very effective agent in the symptomatic treatment of neurotic outpatients. Further research is needed to determine the optimal dosage for placebo therapy. Perhaps dosage intake norms, which probably vary within different treatment settings and social classes, represent a major factor influencing the 'pill effect' on placebo response. 11 references. (Author abstract)

067022 Hussain, M. Z.; Ahad, A. Department of Public Health, Province of Saskatchewan, Moose Jaw, Saskatchewan, Canada Treatment of obsessive-compulsive neurosis. ***Canadian Medical Association Journal (Toronto).*** **103(6):648, 650, 1970.**

In a letter to the editor, commenting on an article by Dr. O'Regan in a previous issue, the authors object that the statement that haloperidol is the most valuable drug in the treatment of Gilles de la Tourette syndrome is not justified since it was made on the basis of the results in 2 patients. The patients' response to treatment varies with each individual. Of 11 recorded cases of very severe chronic obsessive-compulsive neurosis in which psychosurgery was indicated and who were given intensive pharmacotherapeutic trials before a final decision was made, 1 improved on chlorprothixene, 2 on high doses of imipramine (300 to 400mg/day), 2 on high doses of amitriptyline (300 to 400mg/day), 2 on high doses of chlordiazepoxide (up to 100mg/day), and 1 on a high dose of diazepoxide (50mg/day). One patient's illness remitted without medication, and 3 had had haloperidol and triperidol without benefit. Since patients' response to drugs vary, one should try all of the treatments available before a decision is made to performpsychosurgery on these patients. 6 references.

067023 O'Regan, J. B. 113 Palisades, Saskatoon, Saskatchewan, Canada Treatment of obsessive-compulsive neurosis. *Canadian Medical Association Journal (Toronto).* 103(6):650-651, 1970.

In a letter to the editor, commenting on a letter by Drs. Hussain and Ahad in the same issue, the author suggests that there are sufficient clinical features in common between Gilles de la Tourette syndrome and obsessive-compulsive neurosis to suggest that haloperidol which is effective in the treatment of the former, would also be effective in the treatment of latter. Three patients with severe compulsive symptoms have responded well to haloperidol, out of a total of 4 cases of obsessive-compulsive neurosis with symptoms of compulsive ritualistic behavior seen in 3000 patients. It is only in those patients with compulsive rituals that there is any similarity to the Gilles de la Tourette syndrome and in whom haloperidol appears to be effective. Many patients with obsessive-compulsive neurotic symptoms without the ritualistic behavior respond to various chemotherapies, including antidepressants if their complaints are symptomatic of a masked depression. However, haloperidol is the most valuable drug for the treatment of obsessive-compulsive neurosis with compulsive ritualistic symptoms.

11 DRUG TRIALS IN MISCELLANEOUS DIAGNOSTIC GROUPS

065175 Grossman, Herbert J. author address not given Therapy of childhood seizures. *In: Masserman J., Current psychiatric therapies.* New York, Grune and Stratton, 1970. 139 p. (p. 11-25) Vol. 10.

Anticonvulsant drug therapy in the management of childhood epilepsy for which there is no correctible cause is discussed. A chart listing drugs to be used in the various grand mal, petit mal, and focal seizures, their dosages, toxicity, and indications for immediate discontinuance is presented. The clinical management of epilepsy is a dynamic process. Drugs are given initially in arbitrary, minimum doses, which are increased until seizures are controlled or toxic side effects develop. If intoxication appears before control of seizures is achieved, the dosage is reduced and a second drug added. Common mistakes in drug therapy are insufficient trial period, reluctance to increase dosage, sudden withdrawal of a drug when a new one is added, and abrupt discontinuation of anticonvulsant medication. 21 references.

065850 Laurell, Bjorn; Perris, Carlo. Department of Psychiatry, University of Umea, Umea, Sweden Comparison of electric and flurothyl convulsive therapy: I. seizure and post-seizure electroencephalographic pattern. *Acta Psychiatrica Scandinavica.* Supplement 213:8-21, (1970).

Flurothyl (Indoklon) convulsive therapy (ICT) and electroconvulsive therapy (ECT) were compared with regard to seizure and postseizure electroencephalographic (EEG) pattern in a double-blind, intraindividual cross-over design in 12 patients. Treatments no. 2 and 3 were compared. Generalized seizures were elicited by inhalation technique in ICT and by bilateral stimulation in ECT, threshold stimulation being used. The seizure was recorded under practically complete muscular relaxation. The main results were: 1) the average seizure duration was 120 sec. in ICT and 71 sec. in ECT. 2)The seizure pattern had more fast activity and was less synchronized over the brain in ICT. 3) In the post seizure record, which was followed for 30 min.,ICT caused a later appearance and disappearance of alpha, and more globally rated 'abnormality'. The more pronounced EEG disorganization and slower reorganization in ICT indicate a greater functional

disturbance in the central nervous system. The disturbance may be related to the circumstance that the brain by continuous chemical convulsive stimulation is forced to a higher degree of metabolic exhaustion than in ECT. 25 references. (Author abstract)

065855 Laurell, Bjorn. University of Umea, Umea, Sweden Flurothyl convulsive therapy: general discussion. *Acta Psychiatrica Scandinavica (Kobenhavn).* Supplement 213:74-77, 1970.

General comparisons are made between the effects of electroconvulsive therapy (ECT) and flurothyl convulsive therapy (Indoklon) as found in a series of controlled studies. Seizures were more prolonged and posttreatment confusion was greater in the use of ICT. The degree of anterograde amnesia was lower after 1 ICT treatment, but it appears that there would be a cumulative effect and there would be more memory disturbance after a series of ICT treatments than after a series of ECT. Although ICT may have therapeutic advantages in other disorders, there seemed to be no significant difference in antidepression effects. There are no great advantages but some drawbacks in ICT compared to ECT. ICT may be used as an alternative when ECT is contraindicated for physical or psychological reasons. 16 references.

065856 Laurell, Bjorn. University of Umea, Umea, Sweden Flurothyl convulsive therapy. *Acta Psychiatrica Scandinavica.* Supplement 213:1-79, 1970.

An investigation was conducted in order to compare electroconvulsive therapy (ECT) and flurothyl (Indoklon) convulsive therapy (ICT), using minimal doses of flurothyl, with regard to seizure and postseizure, electroencephalograph (EEG) pattern, therapeutic effect in endogenous depression, anterograde and retrograde amnesia, and confusion and other side effects. Intraindividual cross over design or comparison of random groups with double-blind technique was used. The seizure duration, measured by EEG with practically total muscular relaxation, was in ICT on average 70% longer than in ECT. Facts indicate a greater functional disturbance in the central nervous system. The therapeutic efficiency in endogenous depression was fairly similar in groups of patients treated with ECT or ICT. The antegrade effect on the memory variable retention is similar after complete series of ECT and ICT, and may be characterized as a mild and transient Korsakoff syndrome. Retrograde amnesia after the first treatment in a series was lower after ICT. Confusion, operationally defined as reorientation, was more pronounced during the first 2 to 3 hours after ICT, a fact which may be correlated to the prolonged seizure. Other side-effects (headache, drowsiness, nausea), rated by patients and nurses, were fairly similar. From the point of view of antidepressive efficiency and with regard to memory disturbances and other side-effects, ECT and ICT seem to be fairly equivalent. Owing to the technical difficulties in ICT compared to the simple and reliable ECT technique it is reasonable to replace ECT by ICT in the treatment of endogenous depression. However, as an alternative, especially when psychological reasons argue in that direction, ICT may be used instead of ECT. (Author abstract modified)

066806 Rock, Nicholas L. U. S. Army Tripler General Hospital, APO San Francisco, California 96435 Long-term psychotherapy utilizing trifluoperazine in a psychotic preschool child: (a case study). *Diseases of the Nervous System.* 31(8):546-549, 1970.

A case report of a preschool psychotic child is presented where the use of trifluoperazine was used over 1 year. There were reductions in the psychotic behavior, no observable physical damage, and the only adverse reaction was related to exceeding maximum therapeutic dose. This case, and several others now treated with major tranquilizers, in particular trifluoperazine, seem to point to the need to have it used as early in life as possible as it appears to be safe and the results are beneficial enough to warrant its routine use, rather than as a last resort on preschool severely disturbed children. 12 references. (Author abstract modified)

066921 Aagaard, George N. Division of Clinical Pharmacology, University of Washington School of Medicine, Seattle, Washington 98105 Use of drugs in control of chronic pain. *Northwest Medicine.* 69(9):689-692, 1970.

Three factors should be considered in selecting drugs to treat chronic pain: prognosis of the disease, relative effectiveness of the drug and adverse effects of the drug. A good history should be obtained to ascertain the past use of analgesic agents and degree of relief obtained from them. In initiating treatment it is suggested to begin with

modest doses and gradually increase the dose as required and tolerated. Placebo usage may also be important to assess the severity of the pain and progress of the disease. No drug available today is ideal for this treatment of chronic pain. Use of salicylates and non-narcotic analgesics to relieve musculoskeletal pain is discussed. Among these drugs are acetaminophen and phenacetin. Their specific usefulness and toxicities are discussed. The specific properties, advantages and disadvantages of the narcotic analgesics (morphine, codeine, pentazocine, meperidine and propoxyphene) are also discussed. The author recommends use of salicylates to reduce addictive dependence on narcotic drugs. 12 references.

067059 No author. Author address not given In defense of stimulants for hyperkinetic children. *Medical World News.* 11(36):6, 1970.

Despite attempts by the FDA to limit the use of amphetamines for hyperkinetic children, Dr. Mark Stewart of the St. Louis Children's Hospital, still considers them as valid therapeutic agents for these children. In his treatment of several hundred hyperkinetic children, dramatic results were obtained in one half to two thirds. Most of the children treated at the St. Louis facility are given 10 to 20mg methylphenidate per day in divided doses at breakfast and lunch. Those on dextroamphetamine get 5 to 10mg/day. Of the children treated in the psychiatric clinic, only a few have had adverse reactions including headaches, nervousness, vomiting and loss of appetite. No danger of addiction has been found.

12 PSYCHOTOMIMETIC EVALUATION STUDIES

065176 Weiss, Gabrielle. Montreal Children's Hospital, Montreal, Canada Treatment of hyperactivity in children. *In: Masserman J., Current psychiatric therapies.* New York, Grune and Stratton, 1970. 239 p. (p. 26-29) Vol. 10.

The treatment of hyperactivity in children involves: specialized remedial education when learning disorders are present; parental knowledge; a home environment which is structured and provides consistent routines; possible psychiatric care when necessary; and drug therapy. Studies of chlorpromazine, thioridazine, dextromhetamine, and methylphenidate showed the last to be the most effective in reducing restlessness and distractability and symptoms of psychopathology. Since most children tolerate drugs well and respond dramatically to drugs, particularly the stimulants, it is believed that drug therapy should be given a trial in the treatment of every hyperactive child. 9 references.

065433 Landon, M.; Fischer, R. Department of Linguistics, College of Humanities, Ohio State University, Columbus, Ohio 43210 On similar linguistic structures in creative performance and psilocybin- induced experience. *Confina Psychiatrica (Basel).* 13:115-138, 1970.

Samples of the language of creative performance, poetic texts written by W. Whitman under the influence of religious conversion experiences, and samples of the language of creative experience, reportage of prior hallucinatory experiences by volunteers under psilobycin induced arousal were subjected to linguistic analysis. These texts were also compared with others written by the same individuals during nonaroused states. It was found that, during states of ergotropic arousal, whether natural and giving rise to creative performance or drug induced and giving rise to creative experience, variable individuals, those who exhibit large standard deviations on repeated perceptual - behavioral tasks, will produce texts which are very similar in linguistic structure but different from texts written during nonaroused states. Specifically, during ergotropic arousal semantic orientation will be more concrete, syntactic units will be shorter and less complex, rhetorical structure will be modified, and standard deviations on the numerical values of the above criteria will be smaller. These differences are not present in texts obtained under the same conditions but from individuals who exhibit small standard deviations on perceptual - behavioral tasks. 22 references. (Author abstract)

065436 Leonard, B. E.; Tonge, Sally R. Pharmacology Section, I.C.I. Ltd., Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire SK10 4TG, England Some effects of an hallucinogenic drug (phencyclidine) on neurohumoral substances. *Life Sciences (Oxford).* 9:1141-1152, 1970.

Some effects of an hallucinogenic drug, phencyclidine, on neurohumoral substances are observed in an experiment on Wistar rats. The effects of phencyclidine on the concentrations of acetylcholine, cholinesterase, histamine, gamma-aminobutyric acid (GABA) and glutamic acid in

the rat brain were investigated in an attempt to discover whether effects on any of these systems might form parts of a general scheme of hallucinogenic drug activity. Gross behavioral effects of intraperitoneal injections of 10mg/kg of phencyclidine were observed, also. The results revealed that phencyclidine had no effect on the concentrations of acetylcholine, cholinesterase, histamine or glutamic acid. GABA levels appear to be depleted by the drug, but the relationship of excitement, resulting from phencyclidine administration to rats, to GABA levels is not clear and further research appears to be warranted. 29 references.

13 MECHANISM OF ACTION - PHYSIOLOGICAL, BIOCHEMICAL AND PHARMACOLOGICAL

065118 Kane, Francis J.; Lipton, Morris A.; Krall, Albert R.; Obrist, Paul A. Psychiatry Department, University of North Carolina School of Medicine, Chapel Hill, North Carolina 27514 Psychoendocrine study of oral contraceptive agents. *American Journal of Psychiatry.* 127(4):443-450, 1970.

To determine if there was risk of adverse reaction to oral contraceptives, a 2 month single-blind study was made of 7 women who received a combination agent or a sequential agent. All subjects reported affective symptoms; however, significant changes appeared in only 1 patient who was the most clinically disturbed. Catecholamine excretion was altered in all patients. From their findings and the literature, it is speculated that use of such drugs that alter catecholamine metabolism will result in behavioral change, especially in users who have had prior depressive illness. 40 references. (Journal abstract modified)

065183 Blinder, Martin G. Family Therapy Institute, San Francisco, California Lithium carbonate in therapy. *In: Masserman J., Current psychiatric therapies.* New York, Grune and Stratton, 1970. 239 p. (p. 100-104) Vol. 10.

Lithium ion is almost unique as a psychiatric drug: when used knowledgeably, it is effective in perhaps three of four cases, its effects are specific and predictable, it produces virtually no side effects after the first week of administration, and it never causes a 'medication feeling.'Lithium's mechanism of therapeutic action is uncertain, but there is much to suggest that perhaps, as do the affective states themselves, it alters the transport of electrolytes and biogenic amines across the cell membranes of the central nervous system or modifies their intracellular metabolism. Its use in the treatment of recurrent hypomania, recurrent depression, psychotic excitement, premenstrual tension, and anxiety is discussed. 5 references. (Author abstract modified)

065187 Devenyi, Paul. Alcoholism and Drug Addiction Research Foundation, Toronto, Ontario, Canada The treatment of acute alcohol intoxication and withdrawal. *In: Masserman J., Current psychiatric therapies.* New York, Grune and Stratton, 1970. 239 p. (p. 130-134) Vol. 10.

Benzodiazephines, particularly chlordiazepoxide, haloperidol, and chlormethiazole are effective in reducing symptoms. 8 references.0*In: Masserman J., Current psychiatric therapies.*

065187 Devenyi, Paul. Alcoholism and Drug Addiction Research Foundation, Toronto, Ontario, Canada The treatment of acute alcohol intoxication and withdrawal. *In: Masserman J., Current psychiatric therapies.* New York, Grune and Stratton, 1970. 239 p. (p. 130-134) Vol. 10.

The average case of alcohol intoxication can be treated at home with adequate provisions for the patient's safety, the main effort being to interrupt the drinking and provide the opportunity for sleep. Sedatives orBenzodiazephines, particularly chlordiazepoxide, haloperidol, and chlormethiazole are effective in reducing symptoms. 8 references.

065188 Kissen, Benjamin; Gross, Milton M. State University of New York, Downstate Medical Center, Brooklyn, New York Drug therapy in alcoholism. *In: Masserman J., Current psychiatric therapies.* New York, Grune and Stratton, 1970. 239 p. (p. 135-144) Vol. 10.

Drug therapy in the 3 facets of alcoholism (chronic alcoholism, alcohol intoxication, and acute withdrawal syndrome) is discussed in regard to the most effective drugs used. It is felt that the judicious combination of tranquilizers, antidepressants, and disulfiram offers the best pharmacologic program presently available for the long-term treatment of alcoholism. Simple drunkenness is self-limited and requires cessation of drinking and rest. Alcohol stupor or coma requires immediate intravenous administration of glucose. There is no justification for claims concerning drugs that in-

crease the alcohol metabolism rate. Paraldehyde, chlordiazepoxide, barbiturates, and chlormethiazole all appear to be effective agents in the treatment of the withdrawal syndromes. In addition to the aspects of treatment, vitamins, electrolytes, fluids, and treatment of secondary medical complications are elements of major importance. 34 references.

065193 Knott, David H.; Beard, James D. Alcohol Rehabilitation Unit, Tennessee Psychiatric Hospital and Institute, Memphis, Tennessee Diagnosis and therapy of acute withdrawal from alcohol. ***In: Masserman J., Current psychiatric therapies.*** **New York, Grune and Stratton, 1970. 239 p. (p. 145-153) Vol. 10.**

The method of detoxification for acute withdrawal of the delirium tremens variety, which is employed in the Alcoholism Treatment and Research Center, Tennessee Psychiatric Hospital and Institute, follows 6 general guidelines: 1) hydoxyzine (vistaril) 100mg intramuscularly, repeated every 45 to 60 min. for 3 to 4 doses. As a psychotropic this is effective in 75 to 80% of the patients treated. Individuals who present signs and symptoms of a toxic psychosis other than the classical form of acute withdrawal, such as alcohol hallucinosis, receive chlorpromazine (thorazine), 50 to 100mg per dose every 3 to 4 hr. After detoxification, continued drug support for a period of time is often desirable. Initial studies suggest that the new anxiolytic, antidepressant drug doxepin (sinequan) appears to be particularly effective. 2) If overhydration is a complicating factor, diuresis with 1 dose of furosemide (lasix) (40 to 80mg) is effective. 3) To stabilize the blood glucose, 50cc of 50 percent glucose is given intravenously. 4) Thiamine (50 to 100mg) is given parenterally initially, followed by daily oral doses for 30 to 4 days. 5) Diphenylhydantoin (dilantin), 100 mg given 4 times daily and with gradually decreasing dosages for the next 2 to 3 weeks, exerts a salutary effect on the abnormal electrolyte partition associated with acute alcoholism. 6) The infectious diathesis of the acutely withdrawing patient should be recognized and respected. Early and aggressive antibiotic therapy is mandatory. Also, treatment of other coexisting disorders is essential for effective detoxification. 16 references. (Author abstract modified)

065195 Fink Max; Zaks, Arthur; Resnick, Richard; Freedman, Alfred M. Division of Biological Psychiatry, New York Medical College, New York, New York Treatment of heroin dependence with opiate antagonists. ***In: Masserman J., Current psychiatric therapies.*** **New York, Grune and Stratton, 1970. 239 p. (p. 161-170) Vol. 10.**

Based on a conditioning theory of opiate dependence, various substances have been proposed to block the euphoric effects of opiates and reduce dependence by a process of negative reinforcement. Clinical experiences with cyclazocine and n-allylnoroxymorphone indicate that both drugs are effective therapeutic agents. 23 references. (Author abstract)

065418 Cannarsa, D. N. Pfizer Laboratories, New York, N. Y. Drug combinations and interactions. ***Psychosomatics.*** **11(5):526-529, 1970.**

Polypharmacy, or the simultaneous prescription of 2 or more drugs to a patient, is accepted as a necessity in many instances by even its most severe critics. However, the commercial mixtures of 2 or more agents in a fixed strength ratio is now looked upon with unqualified censure. The present discussion considers the causes of the present acute concern over drug combinations by: 1) describing the general mechanisms by which drugs work, and the sequence of possible metabolic pathways that any drug takes; and 2) giving specific examples of drugs whose workings are not only impaired by the effects of other drugs given in combination, but even may have serious consequences for the health of the patient. Because of the impossibility of the practitioner memorizing the enormous number of drugs and their dangerous combinations, and because the interactions of vast numbers of drugs remain still unknown, difficulties seem overwhelming. Laboratory evidence is now helping to elucidate the basic mechanisms of drug interactions. The major burden of the problems rests on the shoulders of the general practitioner who must thread his way through the complexities of modern drug treatment to the potential benefits that they promise. 17 references.

066190 Huisman, J. W.; Van Heycop Ten Ham, M. W.; Van Zijl, C. H. W. Epilepsy Centre 'Meer en Bosch', Heemstede, The Netherlands Influence of ethylphenacemide on serum levels of other antiepileptic drugs. ***Epilepsia.*** **11(2):207-215, 1970.**

In a study of the effect of ethylphenacemide on the metabolism of other antiepileptic drugs, serum phenobarbital, phenytoin and primidone levels

were determined before, during and after addition of ethylphenacemide to the medication of 7 male patients, all with normal liver function and blood counts. During ethylphenacemide medication, a statistically significant increase in levels of phenobarbital and phenytoin in the serum was found. Thus therapeutic and toxic effects of ethylphenacemide may be well due to this secondary action. 9 references. (author abstract modified)

066277 Jarvik, M. E., Glick, S. D.; Nakamura, R. K. Department of Pharmacology, Albert Einstein College of Medicine, New York, New York Inhibition of cigarette smoking by orally administered nicotine. *Clinical Pharmacology and Therapeutics.* 11(4):574-576, 1970.

To determine if maintaining a certain level of nicotine in the blood diminishes the tendency to smoke, five doses per day of 10mg per kilogram of nicotine tartrate were orally administered to 17 volunteers smoking cigarettes ad libitum. Nicotine administration was found to produce a small but significant decrease in the number of cigarettes smoked. 4 references. (author abstract modified)

066399 Hollister, Leo E.; Kanter, Saul L.; Dronkert, Adrian. Veterans Administration Hospital, Palo Alto, California Antidiuresis in man following lysergic acid diethylamide and mescaline. *Behavioral Neuropsychiatry.* 2(3-4):50-54, 1970.

An antidiuretic effect following oral doses of 1.5to 2mcg/kg of lysergic acid diethylamide (LSD-25) was produced in 10 to 14 subjects. As compared with a control day during which a water load was administered, LSD decreased urine formation, decreased free water clearance, and increased urine osmolality. These changes occurred promptly and lasted four hours or more. Determination of serum osmolality and sodium content, or urinary excretion of sodium and chloride, was of no help in demonstrating an antidiuretic effect. Similar changes in urine formation were noted after doses of 5 to 6mg/kg of mescaline, effects being more constant and profound. Attempts to relate the degree of antidiuresis with another measure of physiologic stress, the rise in plasma free fatty acids, or clinical indicators of stress as reported by subjects, were unsuccessful. 7 references. (author abstract modified)

066419 Spiers, A. S. D.; Calne, D. B.; Fayers, P. M. Hammersmith Hospital, Du Cane Road, London W. 12, England Miosis during L-dopa therapy. *British Medical Journal (London).* No. 5710:639-640, 1970.

Pupillary diameters, as a convenient measure of peripheral sympathetic activity, were investigated in 11 patients (aged 47 to 65 years) participating in a trial of L-dopa therapy in idiopathic parkinsonism. The daily doses of L-dopa ranged from 1.0to 6.8g (mean 3.2g). The pupillary diameter of these patients was significantly decreased 4 hours after ingestion of L-dopa. The extent of miosis in individual patients showed no correlation with the dose of L-dopa, the development of hypotension, or the response of the parkinsonism to therapy. It is suggested that this miosis may be caused by diminished noradrenaline output at sympathetic nerve endings, or alternatively, by an action on the central nervous system. 19 references.

066493 Murphy, Dennis L.; Goodwin, Frederick K.; Bunney, William E., Jr. N.I.H. Clinical Center, 10-3-S229, Bethesda, Maryland 20014 Aldosterone and sodium response to lithium administration in man. *Lancet (London)* No. 7618:458-460, 1970.

The possible involvement of aldosterone in the changes in sodium balance accompanying lithium administration was examined in 16 acutely manic and depressed patients. Administration of lithium carbonate (1.2to 1.8g/day) was found to lead to an initial 1 to 2 days of sodium and water diuresis. In the subsequent 4 to 5 day period of treatment, sodium retention associated with a 50% increase in aldosterone excretion occurred, followed in the next several days by a return towards prelithium levels. These changes occurred in all patients and were apparently not related to the initial clinical state of the patient nor the presence or absence of symptomatic improvement with lithium. 20 references. (author abstract modified)

066747 Demers, Robert G.; Heninger, George. Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut Electrocardiographic changes during lithium treatment. *Diseases of the Nervous System.* 31(10):674-679, 1970.

Electrocardiographic changes are studied during lithium treatment of manic-depressive patients. Under controlled conditions, 183 electrocardiograms (EKG's) were obtained from 9 patients while they were on and off lithium. At some point during lithium treatment the tracings of all 9 patients demonstrated T-wave depression, a

phenomena which by analysis of longitudinal data from each was statistically significant in 7 of the 9 patients. No other consistent EKG changes were observed. During lithium treatment one patient had a fall in serum potassium, in the other patients serum electrolytes were normal. In 4 patients where lithium was stopped, T-waves appeared to return to control values. It is concluded that lithium treatment of manic depressive illness is associated with a high frequency of T-wave depression in the EKG which probably represents a benign reversible response of the myocardium to lithium. 11 references. (Author abstract modified)

066875 No author. Author address not given L-dopa in parkinsonism. *Connecticut Medicine.* 34(6):396-398, 1970.

The use of L-dopa in the treatment of parkinsonism is discussed. Improvement in hypokinesia, tremor, and rigidity has been noted in at least 50% of the cases treated with L-dopa, and many of the reported adverse reactions (gastrointestinal intolerance, nausea, and hypotension) have been overcome by slowing the rate of increasing the dose (dyskinesia and delusions are not so easily controlled and may prohibit the use of L-dopa treatment). Insufficient evidence is available to determine whether the gradual downhill course of parkinsonism is altered by L-dopa, but termination of the treatment causes regression to the pretreatment status. The theory that the L-dopa is converted in the brain to dopamine, which then acts as a neurotransmitter in the central nervous system, is substantiated by the ineffectiveness of the drug in some cases (if too many neural pathways are destroyed, the neurotransmitter could not restore them) and the exaggeration of parkinson symptoms by drugs which deplete brain dopamine supplies or increase acetylcholine levels. 2 references.

14 MECHANISM OF ACTION - BEHAVIORAL

064636 No author. Author address not given An ache masking depression. *Medical World News.* 11(39):54H, 1970.

Childhood depression is often associated with migrainous or non-migrainous headache. Twenty five children with a presenting complaint of headache were examined at a neurology clinic, and 10 were diagnosed as suffering from childhood depression, based upon observable behavioral factors. Nine of the 10 patients had exhibited recent mood changes, 8 patients showed signs of social withdrawal and self-deprecation, and 7 of the children complained of sleep disturbances and somatic pains other than headaches, and were deficient in school performance. There was a family history of depression in 9 of the 10 patients, while only 5 of 15 patients not showing symptoms of depression had a family history of depression. A positive family history of depression was determined if a relative had undergone treatment for depressive illness that resulted in prolonged social incapacitation, although neither alcoholism nor suicide alone were considered sufficient criteria for depression. Nine of the 10 depressed patients were treated with the antidepressants amitriptyline and imipramine; 7 showed marked improvement and 2 were slightly improved.

065127 Hurst, P. M.; Radlow, R.; Bagley, Sallyann K. Institute for Research, State College, Pennsylvania Drug effects upon data processing as functions of storage and retrieval parameters. *Ergonomics (London).* 13(4):435-444, 1970.

A series of experiments was performed to investigate the effects of various stimulant and depressant drugs upon performance under task induced stress. The first 4 experiments, each of which included d-amphetanime in one or more dosage, are summarized. This compound was generally the most facilitative of all the drugs tested, but in the fourth experiment reversed its enhancement effect. The fifth experiment, presented in detail, was performed to isolate the crucial task parameters which determine whether d-amphetamine enhances performance or impairs it. To assess futher the relationship between mood and performance effects, sodium amylobarbitone was also given, either alone or in combination with d-amphetamine. Results indicated that the enhancement reversal under amphetamine was specific to high input rates, rather than a function of difficulty per se or of other alternative mechanisms. Amylobarbitone given separately was closely comparable to placebo. When combined with d-amphetamine, it yielded results not significantly different from those of d-amphetamine given by itself, both with performance and with mood ratings. The latter were at variance with published results, and precluded one additional test of the relationship between mood effects and performance under stress. 15 references. (Author abstract)

065852 Laurell, Bjorn. University of Umea, Umea, Sweden Comparison of electric and flurothyl convulsive therapy: III. anterograde amnesia. *Acta Psychiatrica Scandinavica.* Supplement 213:36-50, (1970).

Flurothyl (Indoklon) convulsive therapy (ICT) and electroconvulsivetherapy (ECT) were compared with regard to anterograde effects on memory functions after a complete series of treatments. The design was double-blind and the comparison was made between 2 random groups of patients with endogenous depression, 25 in the ECT and 23 in the ICT group. Cronholm-Molander's memory tests were used and 3 operationally defined memory variables: immediate and delayed reproduction and forgetting were examined the day before the first treatment and 3/7 days after the last treatment. A self-rating of memory was performed on the posttreatment test occasion and 1 month later. The groups were similar with regard to several background variables, number of treatments, clinical effect of the treatment and initial memory scores. The total seizure time was on average 65% longer in ICT. The anterograde effect on memory function concerns mainly the hypothetical variable retention and is about the same after series of ECT and ICT. It is suggested that the longer, forced seizure activity in ICT results in relative hypoxia in the hippocampal mammillary system counteracts the reduction in amnesia from the elimination of the electrical stimulation. 26 references. (Author abstract)

065853 Laurell, Bjorn. University of Umea, Umea, Sweden Comparison of electric and flurothyl convulsive therapy: IV. retrograde amnesia. *Acta Psychiatrica Scandinavica (Kobenhavn).* Supplement 213:51-60, (1970).

Flurothyl (Indoklon) convulsive therapy (ICT) and electroconvulsive therapy (ECT) were compared with regard to retrograde amnesia after a single treatment. The design was double-blind and the comparison was made between 2 random groups, each comprising 24 patients. Generalized seizures were elicited by inhalation technique in ICT and by bilateral stimulation in ECT. Treatment technique was standardized and threshold stimulation used. Cronholm-Molander's memory tests were used and 3 operationally defined memory variables; immediate and delayed reproduction and forgetting were examined on a day before and the day of first treatment. Treatment was given 1 hour after learning. As a measure of retrograde amnesia the difference between the scores of forgetting on the first and second day was used. The groups were similar with regard to several background variables and initial memory scores; the seizure duration was on average 89 sec. in ECT and 114 sec. in ICT. The degree of retrograde amnesia was significantly lower in the ICT group. The result is in accordance with the view that the electric current is of importance for the degree of retrograde amnesia in convulsive therapy. 18 references. (Author abstract)

066231 Hollister, Leo E.; Gillespie, Hamp K. Veterans Administration Hospital, 3801 Miranda Ave., Palo Alto, Calif. 94304 Marihuana, ethanol, and dextroamphetamine: mood and mental function alterations. *Archives of General Psychiatry.* 23(3):199-203, 1970.

In a comparative drug study, 12 normal volunteer subjects were treated with marihuana (median dose equivalent to 32mg tetrahydrocannabinol), ethanol (median dose 57gm), dextroamphetamine (median dose 15mg), and a marihuana placebo. Assignment to treatments was random over weekly intervals. Subjective responses based on a mood scale revealed increased stimulation and activity, as well as decreased drowsiness from dextroamphetamine as compared with placebo; ethanol and marihuana decreased activity. Dextroamphetamine tended to improve performance on psychometric tests; the other 2 drugs tended to impair it. Time estimation was longer with marihuana than with the other treatments, yet because the latter were associated with gross underestimates, marihuana estimates most closely approximated the actual interval being estimated. Dextroamphetamine increased performance on the digit-symbol substitution test. Ethanol and marihuana increased simple reaction time. Marihuana and ethanol were most alike in their effects, with the particular exception of the alteration in time perception produced by the former drug. On the other hand, dextroamphetamine was essentially unlike the other 2 drugs and was the only one which improved, rather than impaired, performance even in nonfatigued subjects. 9 references. (author abstract)

066232 Melges, Frederick T.; Tinklenberg, Jared R.; Hollister, Leo E.; Gillespie, Hamp K. Dept. of Psychiatry, Stanford University School of Medicine, Stanford, Calif. 94305 Temporal disintegration and

***depersonalization during marihuana intoxication.* *Archives of General Psychiatry.* 23(3):204-210, 1970.**

In a study of the temporal and behavioral effects of marihuana, 8 normal men were given a placebo and 20, 40, and 60mg marihuana extract calibrated for content of THC (1-tetrahydrocannabinal). On a cognitive task and a subjective inventory it was found that the oral doses of marihuana extract induced the subjects to confuse past, present, and future and to lose their goal-directedness. This temporal disintegration was related to increases in depersonalization for all 8 subjects. Moreover, for each subject studied separately changes in temporal disintegration correlated positively and substantially with changes in depersonalization; this indicates that these processes were dynamically interrelated. Although each subject showed unique emotional patterns and some had transient adverse reactions, the overall findings indicated that the fragmentation of temporal experience and the accompanying depersonalization were euphorigenic. The euphoria often took place when subjects felt less concerned about future outcomes relevant to maintaining their usual sense self. 18 references. (author abstract modified)

066233 Kales, Anthony; Preston, Terry Anne; Tan, Tjiauw-Ling, Allen, Clyde. UCLA Sleep Research and Treatment Facility, 760 Westwood Plaza, Los Angeles, Calif. 90024 Hypnotics and altered sleep-dream patterns: I. all-night EEG studies of glutethimide, methyprylon, and pentobarbital. *Archives of General Psychiatry.* 23(3):211-218, 1970.

Using a protocol of 8 consecutive nights, 3 hypnotics (glutethimide: 500 and 1000mg; methyprylon: 300mg; and pentobarbital: 100mg) were studied to observe sleep stage and dream alterations and drug effectiveness. Rapid eye movement sleep was decreased in varying degrees by all 3 drugs and dosages. Effects onsleep induction and maintenance, dream reports, comparisons with other studies, and clinical implications are discussed. 18 references. (author abstract modified)

066234 Kales, Anthony; Kales, Joyce D.; Scharf, Martin B.; Tan, Tjiauw-Ling. UCLA Sleep Research and Treatment Facility, 760 Westwood Plaza, Los Angeles, Calif. 90024 Hypnotics and altered sleep-dream patterns: II. all-night EEG studies of chloral hydrate, flurazepam, and methaqualone. *Archives of General Psychiatry.* 23(3):219-225, 1970.

Chloral hydrate (500 and 1000mg), flurazepam (30mg), and methaqualone (150mg), all nonbarbiturate hypnotics, were evaluated using 8 night protocols. The administration of chloral hydrate in both dosages and of 150mg of methaqualone did not result in rapid eye movement (REM) suppression nor did withdrawal produce a REM rebound. Flurazepam (60mg) and methaqualone (300mg) were studied with 3 night and 8 night protocols respectively. Both produced definite REM suppression and withdrawal of methaqualone also produced a REM rebound. The effectiveness of these drugs in inducing and maintaining sleep, however, could not be adequately evaluated in these studies owing to the use of normal subjects who experience little difficulty in falling or staying asleep. Definite trends, however, were established, with 1000mg of chloral hydrate favorably reducing sleep latency and 30mg of flurazepam favorably reducing both sleep latency and wake time after sleep onset. Long-term studies using insomniac subjects with drug administration extending at least 2 weeks are recommended for evaluating the type of drug effectiveness as well as long-term effects on sleep stages. 16 references. (author abstract modified)

066235 Kales, Anthony; Allen, Clyde; Scharf, Martin B.; Kales, Joyce D. UCLA Sleep Research and Treatment Facility, 760 Westwood Plaza, Los Angeles, Calif. 90024 Hypnotic drugs and their effectiveness: all-night EEG studies of insomniac subjects. *Archives of General Psychiatry.* 23(3):226-232, 1970.

Three drugs, chloral hydrate (1000mg), flurazepam (30mg), and glutethimide (500mg), were evaluated in the sleep laboratory with insomniac subjects to determine their effectiveness in inducing and maintaining sleep. A schedule of 22 consecutive nights was used in each separate drug evaluation. Flurazepam (30mg) was found to be effective both in inducing and in maintaining sleep over the entire 2 week drug administration period. Chloral hydrate (1000mg) and glutethimide (500mg) significantly decreased sleep latency on the first set of 3 laboratory drug nights, but this effectiveness appeared to diminish rapidly within several days while the subjects slept at home. This lack of effectiveness was confirmed when the subjects returned to the laboratory. Chloral

hydrate and flurazepam produced only minimal changes in REM (rapid eye movement) sleep. Glutethimide produced a marked REM suppression which persisted throughout the 2 weeks of drug administration. These all night electrophysiological studies demonstrate that the sleep laboratory allows an accurate and objective determination of a drug's effectiveness in inducing and maintaining sleep, the duration of its effectiveness, and the type of sleep induced. This contrasts with traditional studies evaluating drug effectiveness where precise measurements of sleep or waking cannot be made. 6 references. (author abstract modified)

066710 Pangborn, Rose Marie. University of California, Davis, California 95616 Individual variation in affective responses to taste stimuli. ***Psychonomic Science.*** **21(2):125-126, 1970.**

Initial experiments on hedonic responses to the taste of sodium chloride solutions showed that 3 Ss distinctly liked and 5 Ss distinctly disliked increasing concentrations. A paired preference presentation of the same concentrations of sodium chloride resulted in almost identical conclusions for the same Ss, but not with solutions of monosodium glutamate. A second group of 29 Ss demonstrated 3 hedonic distributions to increasing concentrations of sodium chloride and of sucrose--increased dislike, increased liking, or an increase followed by a distinct reduction. 5 references. (Author abstract modified)

066838 Weiss, C. F.; Yaffe, S. J.; Cann, H. M.; Gold, A. P.; Kenny, F. M.; Riley, H. D., Jr.; Schafer, I. Stern, L.; Shirkey, H. C. Author address not given An evaluation of the pharmacologic approaches to learning impediments. ***Pediatrics.*** **46(1):142-144, 1970.**

An evaluation is presented of the use of central nervous system stimulants, tranquilizing agents, and anticonvulsants in treating children with learning impediments or disabilities. Evaluations of this chemotherapeutic approach present problems due to a lack of uniform terminology, marked variability in evaluation methodology, the absence of standardized requirements for precise diagnosis and classification of the symptomatology constituting learning impediments, and the paucity of long-term, properly controlled studies. Studies have indicated some beneficial effect of chemotherapy but numerous variables affect the validity of the conclusions. Double-blind, crossover and/or placebo drug studies are too few in number, and samplings in most instances are too small. The psychological effect of being in a study group must be considered. Test situations which remove a patient from his general environment provide a variable that often results in improvement. More detailed diagnosis should detect underlying organic disease which may affect test results. There is a lack of discrimination between organic and/or psychogenic effects produced by the drugs. There is a need for focus on specific learning problems with a corresponding identification of the influence of a drug on the specific symptom. The effect of the drugs should be compared alone and with adjunctive therapy. 2 references.

066874 No author. Author address not given Drugs, dreams and the coronary patient. ***Connecticut Medicine.*** **34(6):385-386, 1970.**

The effects of drugs on Rapid Eye Movement (REM) sleep is discussed in relation to the coronary patient. During the dreaming part of the sleep cycle, glucocorticoids and catecholamines are released and can initiate myocardial hypoxia in the presence of coronary artery insufficiency. Barbiturates, tranquilizers, and antidepressants reduce the need for REM (and withdrawal of the drug presents no problem) while reserpine, LSD, and l-tryptophan increase REM time. Each drug in itself also has a placebo effect (based on what the patient expects from the drug) which can affect the psychotic nature of the dreams during this sleep cycle. 8 references.

066907 Hussain, M. Z. Union Hospital, Moose Jaw, Saskatchewan, Canada Thiopentone-facilitated implosion in treatment of phobic disorders. ***Canadian Medical Association Journal (Toronto).*** **103(7):768-769, 1970.**

In a letter to the editor the author reports a study of the value of thiopentone facilitated implosion in the treatment of phobic states. The accepted form of therapy to date has been pharmacotherapy or desensitization. Relaxation before and during implosion is achieved by use of slow intravenous infusion of short acting thiopentone in doses sufficient only to produce relaxation. Treatment of 6 phobic patients by this method for 6 to 10 twice weekly 45 minute sessions showed marked suppression of avoidance behavior during implosion. The results and speed of relief were judged superior to other effective treatments. Use of thiopentone reduces the subject's arousal to a

point where he can habituate rapidly to the anxiety evoking stimuli producing rapid extinction. 2 references.

066940 Fehling, Clas; Meier, Manfred J.; Martin, William E. University Department of Neurology, Lund, Sweden Measurement of behavioral changes in patients on L-dopa. *Lancet (London).* No. 7650:786-787, 1970.

In reference to a previous letter to the editor by Drs. Meier and Martin concerning quantitative methods of measuring the effectiveness of L-dopa in Parkinson's disease, Dr. Fehling states that large doses of L-dopa administered orally to parkinsonian patients produce beneficial effects that are strikingly evident, whatever the methods of measurement. In reply Meier and Martin are essentially in agreement but feel that simple, objective, and efficient techniques of documenting the behavioral effects of L-dopa are necessary and again recommend the grooved pegboard task they have developed for this purpose. 5 references.

066954 Battegay, R.; Spiegel, R.; Abt, K. University of Basel, Psychiatric Out-Patient Clinic and Biological and Medical Research Division, Sandoz AG., CH-4000 Basel, Switzerland Comparative pharmacopsychological study of the effects produced by psychopharmaceuticals on verbal interaction in a group of students. *Experientia (Basel).* 26(8):924-927, 1970.

An experiment was designed to measure and assess the effect of psychotropic compounds on the social behavior of clinically normal subjects, and to determine if the effects of two pharmacologically and clinically distinguishable drugs can be distinguished from one another and from a placebo in their action on social behavior. The drugs Desipramine and Thioridazine, and a placebo, were given to six student volunteers in a Latin square dosage design during a six day trial. A modified version of Bales and Slater's interaction analysis was used to evaluate social behavior expressed as verbal activity. Statistical analysis of the data revealed that Desipramine and Thioridazine could not be distinguished from each other or from the placebo in this study, as regards their effects on the verbal activityof the subjects with respect to communicated or received attitudes of friendliness, hostility, and negative and positive attitudes towards themselves and towards others. This study demonstrates the inadequacies that exist in current psychopharmacological methods for evaluating the effects of drugs on normal human behavior. 5 references.

067012 McLeod, W. R.; Carroll, B. J.; Davies, Brian. Department of Psychiatry, University of Melbourne, Royal Melbourne Hospital, Victoria, Australia Hypothalamic dysfunction and antidepressant drugs. *British Medical Journal (London).* No. 5707:480-481, 1970.

Specific drug response, its relation to initial ratings of depression, anxiety, and personality measures, and also the presence or absence of hypothalamic dysfunction were studied in patients with persistent symptoms of primary depressive illness and related in a letter to the editor. After 10 days of supportive care, the patients were given Parnate, 10mg t.d.s. or Tofranil 50mg t.d.s. If significant improvement occurred, identical inert tablets were substituted for the active tablets and progress was observed. Before treatment was started, the midnight dexamethasone test was done. Ten patients suppressed 11-hydroxycorticosteroids normally while 6 patients were nonsuppressors. The 2 groups of patients had similar mean scores of depression, anxiety, and neuroticism. They had the same age and sex distribution. At the end of 1 month, the 10 suppressors were well, all having responded to the particular antidepressant drug and not having relapsed, at the time, with placebo substitution. The 6 nonsuppressors, after 1 month of antidepressant treatment, had not improved and were all then treated with electroconvulsive therapy with subsequent improvement. It is suggested that poor short-term response to antidepressants is related to hypothalamic dysfunction. 3 references.

15 TOXICOLOGY AND SIDE EFFECTS

065232 Newbold, H. L. Asheville, North Carolina Niacin and the schizophrenic patient. *American Journal of Psychiatry.* 127(4):177-178, 1970.

A letter to the editor discusses niacine as used to control schizophrenia, its toxic side effects, and methods of reducing the side effects. These include skin, gastrointestinal, liver, and metabolism changes and excitation of nervous panic states. 3 references.

065409 Schnee, Jack. 109-10 Queens Boulevard, Forest Hills, New York 11375 Pharmacological and dynamic factors in psychotropic drug therapy. *American Journal of Psychoanalysis.* 30(2):169-177, 1970.

In approaching treatment with psychotropic drugs, multiple factors come into play and should be considered. These involve the pharmacology of the drug, including therapeutically desired primary effects as well as so-called side effects, and idiosyncratic sensitivity reactions. Other extra drug factors are concerned with the dynamics of drug therapy. These must be understood in terms of the patient's responses, which are influenced by his personality, and by the influence of the doctor patient relationship. The effect of the environment must be considered as well. This includes the family, and the patient family relationship, as these influence the therapy. All of these factors must be understood and evaluated for their significance and contributions to the total therapeutic situation. 11 references. (Author abstract)

065471 Simpson, George M. Research Center, Rockland State Hospital, East Orangeburg, New York Long-acting, antipsychotic agents and extrapyramidal side effects. *Diseases of the Nervous System.* Supplement 31(9):12-14, 1970.

The concept of long acting drugs is briefly discussed and their usefulness described. The long acting, extrapyramidal side effects are shown to be no different than those of routine antipsychotic drugs, although the onset may be different and the dystonic reactions a little more bizarre. The extrapyramidal effects of the enanthate and the decanoate drugs (of triperidol, butaperazine and fluphenazine) are easily treated; the decanoate is noted to be the longest acting and probably has fewer side-effects. (Author abstract modified)

065854 Laurell, Bjorn. University of Umea, Umea, Sweden Comparison of electric and flurothyl convulsive therapy: V. confusion and other side-effects. *Acta Psychiatrica Scandinavica (Kobenhavn).* Supplement 213:61-73, (1970).

Flurothyl (Indoklon) convulsive therapy (ICT) and electroconvulsive therapy (ECT) were compared with regard to confusion and other side effects in a double-blind, intraindividual cross over design comprising 30 patients. Treatments no. 2 and 3 in the series were compared. Generalized seizures were elicited by inhalation technique in ICT and by bilateral stimulation in ECT, threshold stimulation being used. The main results were: 1) swallowing and spontaneous respiration occurred somewhat earlier after the fit in ICT, but when the longer latency and seizure in ICT was taken into account the difference was reversed. 2) Confusion, measured by operationally defined orientation variables, lasted longer after ICT. 3) Headache, nausea, drowsiness, and memory disturbance as rated by patients and nurses were similar. 4) Global preference rating and preference with regard to separate side-effects showed a slight but insignificant tendency in favor of ECT. The more pronounced postseizure confusion in ICT may be correlated to the longer seizure, which creates a more pronounced functional disturbance in the central nervous system. 31 references. (Author abstract)

066318 Cripps, Derek J.; Peters, Henry A. Section of Dermatology, University of Wisconsin Medical Center, Madison, Wisconsin 53706 Stool porphyrins in acute intermittent and hereditary coproporphyria: adverse effects of tranquilizers. *Archives of Neurology.* 23(1):80-84, 1970.

Hereditary coproporphyria, a rare form of hepatic porphyria with acute intermittent symptoms, is described in an American family. The purpose of this study is to present an additional case and to compare porphyrin excretion, particularly stool porphyrins, in other types of acute porphyria. The proband, a 43 year old man, presented acute neurological symptoms including confusion, personality changes, and symptoms suggesting an acute paranoid schizophrenic reaction, which were precipitated by various unrelated tranquilizers, including meprobamate (Equanil) and chlorpromazine (Thorazine). Urinary porphyrin precursors were increased in the urine and in large quantities in the stool. Stool porphyrins may be of value in distinguishing the 3 forms of hepatic porphyria with acute intermittent symptoms. In the other 2 forms, stool porphyrins were normal or slightly elevated in acute intermittent porphyria and increased, particularly protoporphyrin and hydrophilic X porphyrin, in variegate porphyria. 21 references. (author abstract modified)

066329 Holcenberg, John S.; Halpern, Lawrence M. Department of Medicine, University of Washington, Seattle, Washington 98105 Drug therapy. II. Treatment of drug misuse. *Northwest Medicine.* 69(1):31-33, 1970.

Types of drug abuse and treatment are discussed. In solvent inhalation, the greatest danger stems from suffocation in the plastic bag from which the solvent is inhaled. Treatment requires ventilation and observation of toxic side-

effects in cases of severe, acute intoxication. Marked tolerance and psychologic dependence can occur when using stimulant drugs such as amphetamine. Withdrawal of the habitual amphetamine user presents very serious psychiatric problems. Nonsterile, often communal needle abuse can lead to abscesses, hepatitis, and pulmonary infections. Sedatives, hypnotics and minor tranquilizers present a hazard in that not only is there danger of dependence, but also potential alteration of the metabolism of other drugs. With hallucinogenic drugs, prolonged psychotic delusions, hallucinations and fear reactions occurred at a rate of 0.8per 1000 in an experimental group. More research is necessary on the possible association of chromosomal breaks with LSD. The cure rate of treatment by withdrawal of narcotics was small in a Federal institution; considerable interest has developed in the use of substitution therapy with methadone. Marihuana is more of a social and legal problem than a medical one. 5 references.

066395 DeGross, Joseph. Author address not given Emergency treatment of drug abuse and poison ingestion. ***Resident and Staff Physician.*** **16(2):43-51, 1970.**

Rapid diagnosis and treatment measures for drug overdose and poisoning are presented. Once adequate pulmonary ventilation and tissue perfusion is obtained, further treatment can be performed. Management of specific drugs is discussed including hypnotics, opiates and opiate like drugs, CNS stimulants, psychomimetics, major and minor tranquilizers, anticholinergics, and mixed overdoses.

066490 Jenkins, Ramon B.; Groh, Robert H. Department of Neurology, Washington Hospital Center, Washington, D.C. 20010 Mental symptoms in parkinsonian patients treated with L-dopa. ***Lancet (London).*** **No. 7665:177-180, 1970.**

The high incidence of mental side effects of L-dopa reported in several clinical series and the development of severe, acute psychosis in 2 patients led to a review of mental changes in parkinsonian patients treated with L-dopa. Eighteen of 90 consecutive patients with Parkinson's disease had mental disturbances attributable to therapy with L-dopa. Seven of them became moderately to severely depressed, 4 became suicidal, five became psychotic, and 1 became psychotic and later depressed. One patient developed delusions andhallucinations when L-dopa was temporarily withdrawn. The abrupt appearance and rapid worsening of mental side effects in 5 patients, 3 of whom became suicidal and 2 psychotic, underlines the need for awareness of mental complications of therapy with L-dopa in order to avoid delay in diagnosis and treatment. 15 references. (author abstract modified)

066873 Hughes, S. W. M.; Burley, D. M. Medical Division, CIBA Laboratories, Horsham, Sussex, England Aminoglutethimide: a 'side-effect' turned to therapeutic advantage. ***Postgraduate Medical Journal.*** **46(537)409-416, 1970.**

The occurrence of the endocrine side-effects of goitrogenesis, sexual precocity and virilization during clinical trials of the anticonvulsant, hypnotic drug, aminoglutethimide, led to its withdrawal in 1966. Subsequent investigation revealed that the drug inhibited adrenal biosynthesis of aldosterone, cortisol and androgens, possibly by interfering with the conversion of cholesterol to delta-5 pregnenolone. Aminoglutethimide also modifies the extra adrenal metabolism of cortisol. The possible clinical applications for these side-effects include metastatic and nonmetastatic secreting tumors of the adrenal neoplastic conditions associated with Cushing's syndrome. Other majorindications for therapy with aminoglutethimide are failure of bilateral adrenalectomy for treatment of functional hypercorticism, bilateral adrenal hyperplasia and primary hyperaldosteronism. 54 references.

066890 Daniels, John C. Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut Interactions between certain drugs used preoperatively and anesthetic agents. ***Connecticut Medicine.*** **34(10:708-713, 1970.**

Interactions between various drugs (psychotropics, diuretics and anticholinesterases) and anesthetic agents are discussed along with indicated therapy. The phenothiazines possess antiadrenergic, anticholinergic, antihistaminic and antiserotonin activities. Hypotension can occur during anesthesia following acute or chronic administration of chlorpromazine, especially if there is pre-existing coronary artery or hypertensive cardiovascular disease. Direct acting sympathomimetic amines provide effective treatment. Monoamine oxidase inhibitors (MAO) interact with many drugs including anesthetic agents and barbiturates resulting in prolonged sleeping time,

coma and hypotension. Norepinephrine has been used with success in the treatment of the latter; ultra-short acting barbiturates and muscle relaxants have also been well tolerated. Tricyclic antidepressants interfere centrally and peripherally with the uptake of norepinephrine by sympathetic nerve endings, and, in therapeutic doses, increase pulse rate and blood pressure. These drugs should be withdrawn 3 or 4 days preoperatively. 44 references.

066903 Collins, John. Guy's Hospital, London, S. E. 1, England A case of self-poisoning with Carbrital. ***Postgraduate Medical Journal (London).*** **46(539):584-586, 1970.**

A 67-year-old woman was admitted 1.5hours after taking 50 capsules of carbrital, each containing 100mg pentobarbitone sodium, and 250mg carbromal. On admission she was comatose and areflexic with a pulse of 72/minute, and blood pressure of 90/50mm mercury. Gastric lavage was performed and an intravenous infusion of 0.16 molar sodium lactate and 20mg frusemide was given. For the first 24 hours an alkaline diuresis was maintained. In the second 24 hours, the alkaline diuresis was abandoned, and after 40 hours respiration ceased and atrial fibrillation developed. Cardiac arrest occurred 46 hours after admission, but the patient was restored to sinus rhythm after external cardiac massage and 1 DC countershock of 100 Joules. At 74 hours spontaneous respiration was restored, and consciousness ensued at 90 hours. The patient was discharged 24 days after admission and was scheduled to receive outpatient treatment for depression. Only 104.4mg pentobarbitone was eliminated by the alkaline diuresis. Factors contributing to the cardiac arrest were the high levels of pentobarbitone (2.75mg/100ml plasma), and bromide (6.7mg/100ml), hypothermia with a rectal temperature 89 degrees, and hypokalemia. Conservative management is indicated in the treatment of poisoning with Carbrital. 3 references.

067073 Sacks, O. W.; Kohl, M. Beth Abraham Hospital, Bronx, New York L-dopa and oculogyric crises. ***Lancet (London).*** **No. 7665:215-216, 1970.**

In a letter to the editor, it was noted that of 25 postencephalitic patients placed on L-dopa, 5 patients, who were initially subject to classic oculogyric crises occurring 1 to 7 times weekly, had an initial remission of these crises lasting for 2 weeks to more than 5 months. This was followed by a recurrence of the crises which were at first mild and infrequent, gradually becoming more severe and frequent, and culminating in an intensely severe and almost continuous oculogyric status. An additional patient, who had never had any oculogyric crises before L-dopa administration, developed these in a particularly severe form in the 4th month of drug administration. Among the common accompanying symptoms observed in the oculogyric crises are the following: opisthotonos and generalized rigidity, intense terror and rage, thalamic pain and anguish, multiple autonomic symptoms, agrypnia, complex reiterative movements and twitching, and other symptoms. The ability of the patient to contain the inner violence of these attacks was felt to be due not to voluntary control but to the existence of catalepsy or block, both of which can serve as protective cortical inhibitions in situations of ultimate stress. 5 references.

16 METHODS DEVELOPMENT

066741 Lipman, Ronald S.; Covi, Lino; Rickels, Karl; Derogatis, Leonard R.; Uhlenhuth, E. H. Psychopharmacology Research Branch, National Institute of Mental Health, Barlow Building, Chevy Chase, Maryland 20015 Validation of the MacAndrew-Rosen drug therapy scale. ***Diseases of the Nervous System.*** **31(10):680-683, 1970.**

Data from 3 sources are presented to support the validity of the MacAndrew-Rosen drug therapy scale. It was found that: 1) psychiatrists selected from the community as drug enthusiastic scored reliably higher on the drug therapy scale than did psychiatrists selected as nondrug enthusiastic; 2) both patients' and observing psychiatrists' ratings of doctor drug enthusiasm, after the initial patient visit, were reliably correlated with the treating doctors' MacAndrew-Rosen drug therapy scores. 12 references. (Author abstract)

067074 Mawson, A. B. Maudsley Hospital, London, S. E. 5, England Methohexitone-assisted desensitisation for phobias. ***Lancet (London).*** **No. 7665:217-218, 1970.**

A reply to the points raised by Dr. Hussain and Dr. Hamson regarding a report of a controlled trial of methohexitone assisted desensitization and conventional desensitization with muscular relaxation in the treatment of phobias is presented by the author of that report in a letter to the editor.

It is true that an element of suggestion may be attached to the procedure of intravenous injection, thus contributing to the effectiveness of methohexitone desensitization. However, the injection of an inert substance during the conventional desensitization would have defeated the aim of the work. The methohexitone injection was substituted for relaxation induction by progressive muscular relaxation, not added to it. The suggestion that hypno/autohypnosis might be another alternative to muscular relaxation is interesting. Attention is called to the facts that: 1) methohexitone desensitization is effective even in inexperienced hands; 2) although certain patients are resistant to hypnosis, it is impossible to resist the effects of an intravenous barbiturate; and 3) comparison of hypnosis and conventional systematic desensitization showed the latter to have the advantage. 5 references.

ABSTRACTS

17 MISCELLANEOUS

065346 Bruschi, Walter C. Louisiana State School of Medicine, Shreveport, Louisiana Psychopharmacology and general adaptation syndrome. *Psychosomatics.* 11(5):513-516, 1970.

Mechano-deterministic investigations on the inhibition of ischemic necrosis by chlorpromazine are briefly discussed. The idea is discussed that the living organism is ideally involved in adaptation when it is totally involved. Local breakdowns, such as ischemic necrosis, within the context of teleological determinism, are failures in organismic participation by virtue of faulty alignment to the all encompassing project of adaptation. Psychopharmacology has been able to induce both polarities in adaptation: active involvement and unconditional withdrawal. Psychotropic agents are therefore a temporary blessing to mankind. 12 references.

065459 Lehmann, H. E. McGill University, Montreal, Quebec, Canada The philosophy of long-acting medication in psychiatry. *Diseases of the Nervous System.* Supplement:31(9):7-9, 1970.

The special significance of long acting medication in psychopharmacology is stressed in a discussion of the philosophy of long acting medication in psychiatry. The lack of motivation for treatment so often characteristic of the psychiatric patient and the greater risk involved in leaving psychiatric patients untreated -- risk to themselves and to others in their environment -- are both factors in the particular significance of the long acting preparations used for these patients. For certain specific problems, the long acting antipsychotic drugs represented a major tactical breakthrough. Under regular antipsychotic maintenance treatment, acute patients or those who function well enough to return to the community, may pose no special problem, but providing the needed medication presents serious problems in specific cases. In these, the long acting antipsychotic drugs are of great value. Examples are cited, including certain catatonic and paranoid patients and the patient who has made a good remission but who neglects taking medication for a number of reasons. Legislation, making it mandatory for certain psychiatric patients presenting a danger to the community to obtain the necessary weekly of biweekly injections of a long acting antipsychotic preparation, is suggested. The concern of sociologists could be lessened under such a program.

065472 Capstick, N. Graylingwell Hospital, Chichester, England Long-acting drug treatment in overall psychiatric management. *Diseases of the Nervous System.* Supplement 31(9):15-17, 1970.

The development of modern drug therapy has made community care for acute psychiatric patients and for those discharged from mental hospitals possible. The use of long acting drugs in overall psychiatric management plays an important role. Rehabilitation methods have made possible the discharge of long-term patients from mental hospitals but regular drug therapy is required for continued success of the program. Failure of patients to take medication and the reason for it are documented. Spansules of long acting phenothiazines, requiring medication once in 24 hours, have made the problem less acute, but the further advance to intramuscular administration of long acting preparations which can be given once in periods to 4 weeks, has been a great advantage. The results of a study on inpatients, principally schizophrenics, during long-term administration of fluphenazine enanthate, indicated improvement of varied degree in more than half of the patients. Routine administration of antiparkinsonian drugs was found to be unnecessary. The drugs were given only if side effects were present. It was concluded that fluphenazine enanthate is a potent phenothiazine, and whenever phenothiazines are indicated, clinically, this preparation could be used as an alternative to oral administration. Side effects, if present, could be controlled; administration is, on the average, needed only every 14 days. Management after discharge of the patients is discussed.

066877 No author. Author address not given Doxepin (Sinequan) and other drugs for anxiety and depression. *Connecticut Medicine.* 34(6):456-457, 1970.

Drug therapies for the depression and anxiety symptoms of psychoneuroses, manic-depressive, involutional, and reactive psychoses, schizophrenia, and other mental disorders are reviewed. Sedatives and the phenothiazines have been found effective in relieving anxiety, while amphetamines and tricyclic antidepressants are useful for depression although conflicting results on their efficacy have been reported. Some drugs (amitriptyline, thioridazine, and diazepam) may be effective against both anxiety and depression, and

various combinations of antianxiety and antidepressant drugs may be used as the clinical condition of the patient demands. Doxepin (Sinequan) is currently being studied for its combined antianxiety and antidepressant activity and in one study (Johnstone and Claghorn) was shown more effective than chlordiazepoxide against anxiety while in another study (Rickels) it produced more improvement in the depressive symptoms (when compared with diazepam). Some patients do better on one drug than on another, and more severe cases may also require psychotherapy while less severe cases may flourish on a placebo.

066950 Dally, Peter. Author address not given The present status of psychotropic drugs. *Practitioner (London).* 205(1227):307-312, 1970.

There have been no major advances in the development of psychotropic drugs in the past three years. However, controlled trials of the major tranquilizers, antidepressants and lithium salts have continued to show their efficacy in psychiatric therapy and have clarified their possible modes of action. Barbiturates are still the most effective drugs in severe anxiety, or during a panic attack but the diazepine derivatives, chlordiazepoxide, diazepam and oxazepam, are best for treating chronic and mild forms of anxiety. Propanolol has been used in the treatment of anxiety. Hypnotics such as nitrazepam and chlormethiazole are used for treating patients addicted to barbiturates. The tricyclic antidepressant drugs such as amitriptyline, nortriptyline and trimipramine, are being used for insomnia states, as sedatives in anxiety states, and in mildly depressed anergic patients. Carbamazepine is structurally related to the tricyclic antidepressants and has both anticonvulsant and psychiatric properties. Monoamine oxidase inhibitors such as phenelzine and diazepam are valuable treatments on depressed patients. The main advances in the phenothiazine field is the introduction of long acting forms of fluphenazine for treatment of acute schizophrenia. Haloperidol is used in the treatment of chronic psychotic states and in the treatment of anxiety in older patients. Lithium carbonate is being used for the treatment and prevention of manic-depressive illness. Progesterone is felt to be a more potent cause than estrogen of depression associated with contraceptive pills.